EXHIBIT 18

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ORIGINAL ARTICLE

Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study

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ABSTRACT

Objectives Severe sprue-like enteropathy associated with olmesartan has been reported, but there has been no demonstration of an increased risk by epidemiological studies.

Aim To assess, in a nationwide patient cohort, the risk of hospitalisation for intestinal malabsorption associated with olmesartan compared with other angiotensin receptor blockers (ARB) and ACE inhibitors (ACEIs).

Design From the French National Health Insurance claim database, all adult patients initiating ARB or ACEI between 1 January 2007 and 31 December 2012 with no prior hospitalisation for intestinal malabsorption, no serology testing for coeliac disease and no prescription for a gluten-free diet product were included. Incidence of hospitalisation with a discharge diagnosis of intestinal malabsorption was the primary endpoint.

Results 4 546 680 patients (9 010 303 person-years) were included, and 218 events observed. Compared with ACEI, the adjusted rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption was 2.49 (95% CI 1.73 to 3.57, p<0.0001) in olmesartan users. This adjusted rate ratio was 0.76 (95% CI 0.39 to 1.49, p=0.43) for treatment duration shorter than 1 year, 3.66 (95% CI 1.84 to 7.29, p<0.001) between 1 and 2 years and 10.65 (95% CI 5.05 to 22.46, p<0.0001) beyond 2 years of exposure. Median length of hospital stay for intestinal malabsorption was longer in the olmesartan group than in the other groups (p=0.02). Compared with ACEI, the adjusted rate ratio of hospitalisation for coeliac disease was 4.39 (95% CI 2.77 to 6.96, p<0.0001) in olmesartan users and increased with treatment duration.

Conclusions Olmesartan is associated with an increased risk of hospitalisation for intestinal malabsorption and coeliac disease.

Significance of this study

What is already known on this subject?
- Cases of olmesartan-induced severe sprue-like enteropathy have been reported.
- The reality of the association has been questioned.
- It is also unknown whether there is an association between enteropathy and other angiotensin receptor blockers (ARBs).

What are the new findings?
- In this large nationwide observational patient cohort, olmesartan exposure is associated with an increased risk of hospitalisation for intestinal malabsorption and coeliac disease.
- This relative risk increases with treatment duration.
- We found no such risk for other ARBs.

How might it impact on clinical practice in the foreseeable future?
- Patients and physicians, including gastroenterologists, should be widely informed of this severe complication.

INTRODUCTION

Olmesartan is an angiotensin II receptor blocker (ARB); its prodrug, olmesartan medoxomil, has been first approved in 2002 in the USA and in 2003 in the European Union, for the treatment of hypertension. Severe sprue-like enteropathies associated with olmesartan have recently been reported.[1 2] The first case series included 22 patients. These patients had severe, chronic diarrhoea and weight loss. Duodenal biopsies showed villous atrophy and inflammation. Coeliac disease serology was negative, and gluten-free diet was ineffective. All patients had taken olmesartan for several months or years. Olmesartan withdrawal was followed by clinical and, when assessed, histological improvement. Nine additional case reports and one literature review have been published[3–8] and confirmed these findings. Olmesartan seems to account for a significant proportion of non-coeliac sprues. In a series of 72 adult patients with villous atrophy and negative coeliac disease serology, olmesartan was prescribed in 16 of these patients, and all but one obtained clinical improvement after olmesartan discontinuation.[9] More recently, a new series of 39 patients with olmesartan-associated sprue has been reported.[10] Interruptions and reintroductions could be studied in a subgroup of 12 patients. Interruptions were followed by remissions, and reintroductions were followed by relapses. These reports suggest that olmesartan may cause severe enteropathy. However, the level of evidence of case reports and small series is limited. The association between olmesartan and enteropathy has also been questioned, as the ROADMAP trial, a

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large randomised controlled trial with several years of follow-up, did not demonstrate any difference in diarrhoea or GI event rates between olmesartan and placebo.[11–13] However, in 2011, the FDA requested a Mini-Sentinel modular programme report of risk assessment because the number of cases of coeliac disease among users of olmesartan was higher than expected in the FDA Adverse Event Report System. The incidence of coeliac disease was found to be similar among all ARBs, including olmesartan.[14 15] Nevertheless, in July 2013, the FDA issued a 'Drug Safety Communication' approving a label change to include sprue-like enteropathy linked to olmesartan.

The association between olmesartan and enteropathy needs to be further investigated. The causality of the association remains uncertain, and its magnitude has not been determined. Moreover, it is unknown whether the association between enteropathy and ARB is limited to olmesartan or also includes other ARBs.

The objective of this study was to assess the risk of enteropathy associated with olmesartan. However, no specific diagnosis code is available for this disease, which was unknown prior to the first published case series. We, therefore, assessed the risk of intestinal malabsorption and coeliac disease associated with the prescription of olmesartan. For this purpose, we compared the rates of hospitalisation with a discharge diagnosis of intestinal malabsorption in patients who were prescribed olmesartan, other ARBs and ACE inhibitor (ACEI) in a large nationwide patient cohort.

METHODS

Data sources

The SNIIRAM (*Système National d'Information Interrégimes de l'Assurance Maladie*) is the French National Health Insurance anonymised claim database. Claims from the general health insurance scheme were used in this study. They include 51.3 million of the 65.7 million inhabitants of France (2013 census), and are available since 2006. Anonymised patient-level records contain billable claims and sociodemographic data such as age and sex. Billable claims include dispensed drugs, laboratory tests (without their results), medical procedures and ambulatory medical care. This database has been previously described.[16 17]

The French hospital discharge database programme médicalisé des systèmes d'information (PMSI) contains information about each patient admitted to a public or private hospital in France, including inpatients and outpatients. This database contains information such as discharge diagnosis (recorded by International Classification of Diseases 10 (ICD-10) code), comorbidities, age, sex, diagnosis-related group, medical procedure performed and length of stay.[16–18]

These two databases were linked in the present study in order to correlate drug prescription with hospitalisation rates and diagnoses. This study was approved by the French data protection agency (*Commission Nationale de l'Informatique et des Libertés*). All databases used in this study only contained anonymous patient records.

Study population

A cohort was constructed from the SNIIRAM, including all adult patients who initiated treatment with an ACEI or ARB between 1 January 2007 and 31 December 2012. The first filled prescription of ACEI or ARB during this period of time constituted the entry date in the cohort (index date). Patients had to be enrolled in the database for at least 1 year before the index date to prevent left censoring. To ensure the absence of left censoring, patients were required to have at least one recorded claim of any type, 1–2 years before the index date. In order to limit the study to incident users of studied drugs, we excluded patients who had filled a prescription containing ACEI or ARB during the 12 months before the index date. Patients with at least one of the following criteria were also excluded: (1) hospitalisation with a discharge diagnosis of intestinal malabsorption (ICD-10 codes K90x) during the year before the index date, (2) any filled prescription containing a gluten-free diet product during the year before the index date, (3) any reimbursed coeliac disease-specific serological testing during the year before the index date.

The ICD codes of coeliac disease and malabsorption were considered as proxies for the diagnosis of olmesartan-associated sprue. It was, therefore, necessary to exclude patients with history of intestinal malabsorption before index date and/or patients with coeliac disease. Therefore, patients who had undergone serological testing or had received gluten-free diet or had been hospitalised with a discharge diagnosis of intestinal malabsorption before the index date were excluded.

Outcomes

The primary outcome was hospitalisation with a discharge diagnosis of intestinal malabsorption (ICD-10 codes K90x). The secondary outcome was hospitalisation with a discharge diagnosis of coeliac disease (ICD-10 code K90.0). Patients were censored at the first event, death or end of the study (31 December 2012 in the main analysis and 31 May 2012 in the sensitivity analysis to avoid information bias).

Exposure assessment

Three kinds of exposures were studied: exposure to olmesartan, exposure to other ARB and exposure to ACEI. Exposure was defined as follows for these three groups. It started from the date of a filled prescription containing a drug of interest (ie, olmesartan, other ARB or ACEI). The end of exposure was defined as the end of prescription duration plus a grace period of 30 days. Grace period is commonly used and recommended in pharmacoepidemiological studies based on claim databases in order to account for incomplete medication adherence and avoid underestimation of drug exposure or misattribution of events. Patient could simultaneously fall into several exposure categories (eg, ACEI+olmesartan). Such periods of overlapping exposure to different drug class were removed from the analysis to prevent misattribution of events. However, they were accounted for in the calculation of treatment duration to prevent classification bias.

Statistical methods

For the primary outcome, a Poisson regression model adjusted for the following potential confounders was used: age, sex, heart failure, dementia, diabetes, immune-mediated diseases (rheumatoid arthritis, Hashimoto thyroiditis, IgA deficiency, dermatitis herpetiformis, lupus, Sjogren, dermatopolymyositis, complement deficiency, angioedema, IBDs), transplantation, ongoing cancer and renal failure. The comorbidities were based on the diagnoses, medical procedures and drug prescriptions from the PMSI and the SNIIRAM.

For the secondary outcome (hospitalisation with a discharge diagnose of coeliac disease), the Poisson regression model was adjusted for age, sex and the following comorbidities: heart failure, diabetes, immune-mediated diseases (rheumatoid arthritis, Hashimoto thyroiditis, IgA deficiency, dermatitis herpetiformis, lupus, Sjogren, dermatopolymyositis, complement deficiency, angioedema, IBDs), active cancer and renal failure.

Dementia and transplantation were removed because of a lack of events. We adjusted for these comorbidities for the following reasons. Patients with immune-mediated abnormalities are at increased risk for coeliac disease. Patients with cancer or allograft recipients are often prescribed drugs that may provoke diarrhoea and malabsorption. Patients with dementia are commonly treated differently from other patients regardless of the disease. Diabetes is a common cause of GI symptoms, including diarrhoea (autonomous neuropathy). Renal failure and heart failure may have influenced the choice of antihypertensive drug.

Poisson regression model fit was assessed by overdispersion analysis, using the deviance/number of degree of freedom ratio and the Pearson χ^2 statistic. Medians were compared by the multisample median test (Brown–Mood test), which assigns 1 for observations greater than the median, and 0 otherwise, and produces χ^2 statistics.[19] Data management and statistical analyses were performed with SAS Enterprise Guide V.4.3.

RESULTS

Study population

A total of 4 552 130 patients initiating ARB or ACEI treatment between 2007 and 2012 were selected from the database; 154 patients who had been hospitalised for intestinal malabsorption during the 12 months preceding inclusion and 4611 patients who had undergone coeliac disease serology testing during the past 12 months were excluded. Finally, 685 patients with a reimbursement claim for a gluten-free diet product in the past 12 months were also excluded. A total of 4 546 680 patients corresponding to 9 129 149 person-years (PY) were included: 118 846 PY of multiple exposures were excluded from the analysis and the remaining 9 010 303 PY of single treatment exposure were distributed as follows: 3 646 311 PY of ACEI exposure, 860 894 PY of olmesartan exposure and 4 503 098 PY of other ARB exposure. The inclusion flow chart is presented in figure 1.

Baseline patient characteristics are presented in table 1. Mean age at inclusion was 63.9 years in the ACEI group, 61.3 years in the olmesartan group and 62.3 years in the other ARB group. The ACEI group comprised fewer women (45.6%) than the olmesartan group (53.9%) and the other ARB group (55.6%). The Poisson regression model was adjusted for both age and sex.

Seventy-seven per cent of the PY in the olmesartan group were included during the 2010–2012 period compared with 72% in the ACEI group and 70% in the other ARB group. Median duration of treatment exposure varied from 326 days (ACEI) to 348 days (olmesartan) and 514 days (other ARBs).

No coding trend of hospital discharge diagnoses of intestinal malabsorption was observed over the study period (see online supplementary table S2).

Incidence of severe malabsorption and coeliac disease

Two hundred eighteen hospitalisations for intestinal malabsorption were observed, 87 in the ACEI group, 48 in the olmesartan group and 83 in the other ARB group, yielding crude incidence rate of 2.4 per 100 000 PY, 5.6 per 100 000 PY and 1.8 per 100 000 PY, respectively.

Olmesartan was associated with an adjusted rate ratio of 2.49 (95% CI 1.73 to 3.57, p<0.0001) of hospitalisation with a discharge diagnosis of intestinal malabsorption compared with ACEI and a rate ratio of 3.17 (95% CI 2.22 to 4.53, p<0.0001) compared with other ARBs. ARBs other than olmesartan were associated with a non-significant rate ratio of 0.78 (95% CI 0.58 to 1.07, p=0.12) of hospitalisation with a discharge diagnosis of intestinal malabsorption, compared with ACEI. Women had a higher rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption (rate ratio 1.42, 95% CI 1.08 to 1.87, p=0.01). Inclusion of an interaction term between sex and treatment was added to the model, but was not significant, and was, therefore, not kept in the multivariate model. Gender-stratified results were also calculated. We found no difference between men and women (data not shown). Age had no influence on this rate ratio.

Median length of hospital stay was longer in the olmesartan group (9 days) than in the other ARB group (2 days) and the ACEI group (4 days) (p=0.02).

Hospitalisations with a discharge diagnosis of coeliac disease (ICD-10 code K90.0) were also studied, as olmesartan-associated enteropathy mimics coeliac disease. Adjusted rate ratio of hospitalisation with a discharge diagnosis of coeliac disease was 4.39 (95% CI 2.77 to 6.96, p<0.0001) in patients who were prescribed olmesartan compared with those who were

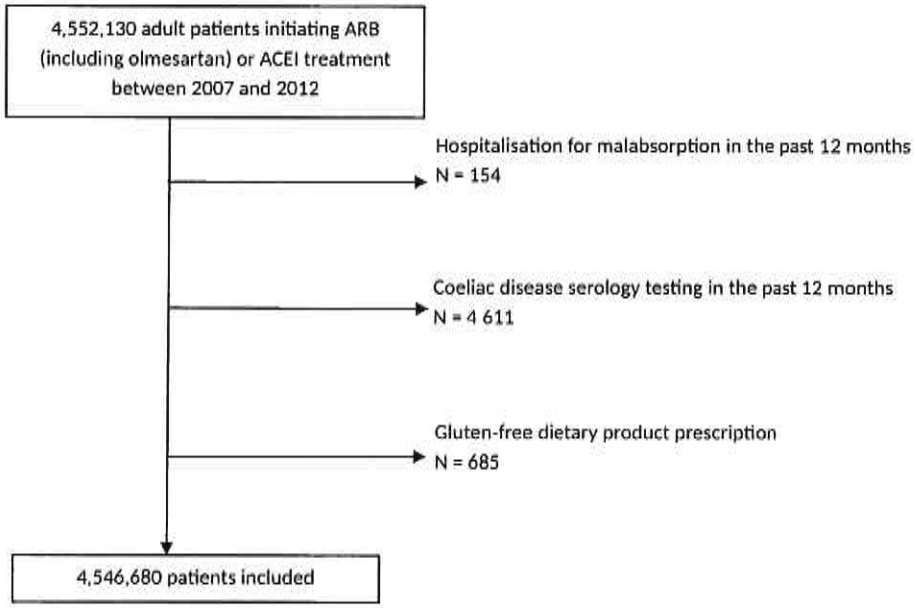

Figure 1 Inclusion flow chart. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

Table 1 Population characteristics

	ACEI			Other ARBs			Olmesartan		
	Number of PY	Per cent	Number of events	Number of PY	Per cent	Number of events	Number of PY	Per cent	Number of events
Total	3 646 311	100	87	4 503 098	100	83	860 894	100	48
Women	1 662 055	45.6	40	2 504 538	55.6	59	464 166	53.9	31
Age									
18–39 years	117 367	3.2	8	145 315	3.2	2	30 515	3.5	1
40–49 years	373 726	10.2	8	495 596	11.0	13	108 604	12.6	6
50–59 years	822 079	22.5	22	1 082 446	24.0	13	227 431	26.4	7
60–69 years	921 633	25.3	25	1 195 828	26.6	19	235 147	27.3	12
70–79 years	788 347	21.6	14	975 638	21.7	24	172 525	20.0	14
≥80 years	623 159	17.1	10	608 274	13.5	12	86 672	10.1	8
Inclusion year									
2007	123 472	3.4	3	165 809	3.7	4	22 987	2.7	1
2008	337 993	9.3	17	461 097	10.2	9	66 881	7.8	1
2009	544 289	14.9	12	706 453	15.7	18	111 884	13.0	3
2010	729 240	20.0	23	906 922	20.1	21	161 780	18.8	10
2011	878 875	24.1	13	1 067 364	23.7	13	216 958	25.2	18
2012	1 032 443	28.3	19	1 195 453	26.5	18	280 405	32.6	15

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; PY, person-years.

prescribed ACEI and 4.82 (95% CI 3.12 to 7.45, p<0.0001) compared with other ARBs. This ratio was 0.91 (95% CI 0.58 to 1.42, p=0.68) in patients who were prescribed other ARBs compared with those who were prescribed ACEI. See table 4 for details.

The first case report linking olmesartan and enteropathy was published online on 25 June 2012. We, therefore, performed a sensitivity analysis in which the study period and follow-up ended on 31 May 2012, which gave very similar results (see online supplementary tables S3–S5).

Risk over time

Descriptive data were in favour of non-homogeneity of risk according to the duration of treatment exposure (table 2). To account for such changes in risk and to assess the kinetics of the risk of hospitalisation with a discharge diagnosis of intestinal malabsorption associated with olmesartan exposure, the model was stratified on treatment exposure. The following duration strata were used: less than 1 year, between 1 and 2 years, and 2 years or more. Compared with ACEI, the adjusted rate ratio of hospitalisation with a discharge diagnosis of intestinal malabsorption associated with olmesartan exposure was 0.76 (95% CI 0.39 to 1.49, p=0.43) for treatment duration shorter than 1 year, 3.66 (95% CI 1.84 to 7.29, p<0.001) between 1 and 2 years of treatment exposure and 10.65 (95% CI 5.05 to 22.46, p<0.0001) beyond 2 years of treatment exposure (table 3). Very similar results were obtained when follow-up ended on 31 May 2012 (see online supplementary tables S4 and S5). Compared with ACEI, the rate ratio of hospitalisation with a discharge diagnosis of coeliac disease was 1.98 (95% CI 0.85 to 4.61, p=0.11) for treatment shorter than 1 year; 4.36 (95% CI 2.04 to 9.34, p<0.001) for treatment between 1 and 2 years and 10.21 (95% CI 4.21 to 24.76, p<0.0001) for more than 2 years of olmesartan exposure (table 4). Details of discharge diagnoses by duration of treatment exposure in each group are presented in online supplementary table S1. No overdispersion was observed in any Poisson regression models.

Table 2 Risk over time: descriptive data

	ACEI	Olmesartan	ARB
PY	3 646 311	860 894	4 503 098
0–1 year	1 584 921	377 748	1 706 722
1–2 years	922 124	223 477	1 153 054
≥2 years	1 139 266	259 668	1 643 322
Number of events	87	48	83
0–1 year	59	10	36
1–2 years	18	15	23
≥2 years	10	23	24
Crude incidence rate (per 100 000 PY)	2.39	5.58	1.84
0–1 year	3.72	2.65	2.11
1–2 years	1.95	6.71	1.99
≥2 years	0.88	8.86	1.46

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; PY, person-years.

DISCUSSION

In this large nationwide cohort of patients, olmesartan users were found to have an increased risk of hospitalisation for intestinal malabsorption and coeliac disease compared with ACEI. These risks increased with duration of olmesartan exposure up to 10-fold beyond 2 years of exposure. Users of ARBs other than olmesartan did not exhibit an increased risk of hospitalisation for intestinal malabsorption or coeliac disease. These results were adjusted for potential confounders. During the first year of treatment, patients treated with other ARBs had a decreased rate of hospitalisation for intestinal malabsorption compared with patients treated with ACEI. There was an excess of diagnoses of malabsorption other than coeliac disease among ACEI users (ICD-10 codes K90.4, K90.8 and K90.9; see online supplementary table S1). However, no significant difference in terms of risk of hospitalisation for coeliac disease (ICD-10 code K90.0) was observed between users of ARBs other than olmesartan and ACEI users. The reason for this is unclear, but it does not affect the consistency of the results. It may have

Table 3 Crude and adjusted rate ratios of hospitalisation with a discharge diagnosis of intestinal malabsorption over time (ref: ACEI)

	Crude rate ratio	95% CI	p Value	Adjusted rate ratio	95% CI	p Value
Overall population						
Olmesartan	2.34	(1.64 to 3.32)	<0.0001	2.49	(1.73 to 3.57)	<0.0001
Other ARBs	0.77	(0.57 to 1.04)	0.09	0.78	(0.58 to 1.07)	0.12
Treatment duration <1 year						
Olmesartan	0.71	(0.36 to 1.39)	0.32	0.76	(0.39 to 1.49)	0.43
Other ARBs	0.57	(0.37 to 0.86)	0.007	0.58	(0.38 to 0.88)	0.01
Treatment duration 1–2 years						
Olmesartan	3.44	(1.73 to 6.82)	0.0004	3.66	(1.84 to 7.29)	<0.001
Other ARBs	1.02	(0.55 to 1.89)	0.95	1.03	(0.56 to 1.92)	0.92
Treatment duration >2 years						
Olmesartan	10.09	(4.80 to 21.20)	<0.0001	10.65	(5.05 to 22.46)	<0.0001
Other ARBs	1.66	(0.80 to 3.48)	0.18	1.68	(0.80 to 3.51)	0.18

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

underestimated the rate ratio associated with olmesartan as compared with ACEI.

The strength of the association and the consistency with reported cases (including the long lag time between initiation of olmesartan and diagnosis of malabsorption) are strong arguments in favour of causality. In addition, the longer length of hospital stay in patients who were prescribed olmesartan suggests that their disease was distinct from and more severe than that observed in patients receiving ARBs or ACEI. Patients who obtained clinical improvement after stopping olmesartan and who experienced subsequent recurrence of symptoms on olmesartan rechallenge have also been described.[6 7] In the aforementioned ROADMAP trial, no significant difference in the rate of GI adverse events or diarrhoea was observed between olmesartan and placebo.[10–12] However, these adverse events are common in patients with diabetes (reported in 3.5% and 2.3% of patients in the olmesartan arm of this trial, respectively), and may have confounded the effect of olmesartan on the risk of severe enteropathy. This more specific risk was not assessed in this trial, which did not have sufficient statistical power to detect such an association. For the same reasons, a recent cohort study did not find any significant difference in the risk of GI disease-related hospitalisation among patients with diabetes treated by olmesartan compared with patients with diabetes treated by other ARBs.[20]

Table 4 Adjusted rate ratios of hospitalisation with a discharge diagnosis of coeliac disease (ref: ACEI)

	Adjusted rate ratio	95% CI	p Value
Overall population			
Olmesartan	4.39	(2.77 to 6.96)	<0.0001
Other ARBs	0.91	(0.58 to 1.42)	0.68
Treatment duration <1 year			
Olmesartan	1.98	(0.85 to 4.61)	0.11
Other ARBs	1.07	(0.56 to 2.05)	0.84
Treatment duration 1–2 years			
Olmesartan	4.36	(2.04 to 9.34)	<0.001
Other ARBs	0.77	(0.36 to 1.67)	0.51
Treatment duration >2 years			
Olmesartan	10.21	(4.21 to 24.76)	<0.0001
Other ARBs	0.94	(0.36 to 2.47)	0.90

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

This study has several strengths. First, it was based on a large nationwide database. Second, we adjusted for potential confounders that may affect the outcome (hospitalisation with a discharge diagnosis of malabsorption) or the prescription of antihypertensive drugs. Finally, to prevent selection bias, we excluded those patients with malabsorption and those at risk for coeliac disease before the index date.

Several potential limitations of this study should also be discussed. First, this study was based on administrative data, which may result in information bias. There is no direct comparison between these data and chart review in France for the diagnosis of intestinal malabsorption or coeliac disease. However, the possible lack of sensitivity is unlikely to affect the three groups of the study differently; as such, it does not result in bias in the analysis, and could not refute the message of the study. Another issue raised by healthcare electronic records concerns trends in coding practice. However, in this study, no coding trend was observed for intestinal malabsorption among adult patients in France during the study period (see online supplementary table S2). Second, the potential indication bias should be discussed. However, ACEI and ARB share very similar therapeutic indications. Coeliac disease is more frequent in women and in younger subjects,[21] but analyses were adjusted for age and sex. In addition, there is no reason why coeliac disease-predisposing HLA genotype would be overrepresented in patients who were prescribed olmesartan. Finally, it is unlikely that all cases of olmesartan-associated enteropathy were captured by hospital diagnoses of intestinal malabsorption and coeliac disease. It is likely that milder forms also exist. Overall number needed to harm was 31 350 patient-years of olmesartan exposure. Beyond 2 years of exposure, this number was 12 500 patient-years. However, caution is needed to interpret these values as this study was not aimed to measure the incidence of olmesartan-associated enteropathy, but rather to estimate the strength of the association between olmesartan and severe forms of enteropathy and malabsorption. As a consequence, this study underestimates the true incidence and only provides the incidence of the most severe forms of olmesartan-associated enteropathy.

In summary, this paper shows, with a higher level of evidence, the association between severe intestinal malabsorption and olmesartan exposure. These results have important practical consequences as olmesartan is widely prescribed worldwide. In France, olmesartan was prescribed to more than 800 000 patients in 2012. Patients treated with olmesartan should be informed about the risk of this complication, and should be

advised to seek medical attention if they experience GI symptoms. This information should also be widely delivered to physicians of all disciplines, particularly to gastroenterologists who are faced to this new category of patients.

However, further studies are required to assess the frequency and clinical spectrum of milder forms. The pathophysiology of olmesartan-associated enteropathy also requires further investigation: the clinical and pathological features are remarkably similar to those of coeliac disease or refractory sprue, but the underlying cause and mechanisms are different. We expect such studies to shed new light on coeliac disease.

Contributors FC and HA had the idea for the study. MB conceived and planned the study and drafted the manuscript. MM performed data management and statistical analyses. All authors contributed to interpretation of the data and revised the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

Ethics approval This research was authorised by the French Data Protection Agency (CNIL).

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Data sharing statement FC had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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GUT

Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study

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EXHIBIT 19

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NOT FOR PUBLICATION
United States District Court, D. New Jersey.

Sandra GEISS and Robert Geiss h/w, Plaintiffs,
v.
TARGET CORPORATION and/or Target Corporation of Minnesota, John Does 1–5 (fictitious persons) and ABC Corps 1–5 (fictitious corporations), Defendants/Third Party Plaintiff(s),
v.
Virtua Memorial Hospital, Virtua Memorial Hospital—Mt. Holly, Virtua West, John Does 1–10 (names unknown) and ABC Corps 1–10 (names unknown), Third Party Defendant(s).

Civil No. 09–2208 (RBK/KMW).
|
Aug. 30, 2013.

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OPINION

KUGLER, District Judge.

*1 This matter comes before the Court upon the motion of Target Corporation ("Target") for partial summary judgment, pursuant to Federal Rule of Civil Procedure 56, against Sandra and Robert Geiss ("Plaintiffs"). Virtua Memorial Hospital ("Virtua"), a third party defendant in this case, also now moves for summary judgment. For the reasons expressed herein, Target's motion for summary judgment is **DENIED.** However, Virtua's motion for summary judgment is **GRANTED.**

I. FACTS AND PROCEDURAL HISTORY

According to Plaintiffs, this matter arises out of a fall that Plaintiff Sandra Geiss sustained at a Target store in Burlington, New Jersey. Because Plaintiff's medical history and post-fall treatment are relevant to the conflicting theories of causation advanced by both parties, the Court will provide a detailed background to this case. Although the Court presents a composite of facts from Plaintiffs, Target, and Virtua, the Court will construe all facts in the light most favorable to the non-moving parties, as it must at this stage in the litigation.

In January 2006, Plaintiff underwent knee replacement surgery in which her right knee joint was removed and replaced with a prosthetic component. Target's Mot. Summ. J., Ex. P–1 at 1. Plaintiff alleges that on July 25, 2007, she tripped over an uneven rug while passing through the entrance of the Burlington, NJ Target store, landing on her stomach and knees. *Id.*, Ex. B at 2; Target's Statement of Undisputed Material Facts ("SUMF"), ¶ 2. Plaintiff did not experience immediate pain on the day of her fall, but days later developed increasing pain in her right knee and required a cane and walker to ambulate. *Id.*, Ex. T at 33–40. On August 2, 2012, Plaintiff visited her primary care physician, Dr. Chatyrka, complaining of right knee pain. Target's SUMF, ¶ 3. Dr. Chatyrka determined that Plaintiff was suffering from sciatica and recommended that she obtain an X-ray of her right knee. Target's Mot. Summ. J., Ex. C. The X-ray indicated that the prosthetic components were properly positioned and undamaged, but also revealed a fluid collection of unknown origin. *Id.*, Ex. D.

On August 17, 2012, Dr. Schoifet, the orthopedic surgeon who performed Plaintiff's knee replacement in 2006, examined Plaintiff's knee. *Id.*, Ex. E. Dr. Schoifet noted Plaintiff's complaints of increasing knee pain, but found that Plaintiff had no instability in her knee and confirmed that the X-ray demonstrated good positioning of the prosthetic components. *Id.*; Target's SUMF, ¶ 5–6. He ultimately concluded that Plaintiff suffered a right knee contusion as a result of her fall. *Id.*

On August 29, 2012, Plaintiff Sandra Geiss presented to Virtual Memorial Hospital complaining of "back pain, leg pain, numbness, pain radiating from back into legs and extreme pain when ambulating." Pls.' Supplemental Statement of Disputed Material Facts ("SDMF"), ¶ 7. A few hours after Plaintiff's arrival, tests revealed that Plaintiff had an elevated white blood cell count, elevated

blood pressure, high blood sugar, and a high temperature. Target's Mot. Summ. J. at 4; *see also* Ex. F at 6–8. Soon thereafter, Plaintiff was diagnosed with hypoxia and pneumonia. *Id.*, Ex. F at 9. Plaintiff was admitted to the hospital, and then to the Intensive Care Unit, where she was intubated. *Id.*, Ex. I at 2. Blood cultures also revealed that Plaintiff had MSSA (Methicillin–Sensitive Staphylococcus Aureus), a bacterial infection. *Id.* Plaintiff spent some time in the ICU in order to receive treatment for her various ailments and to stabilize her condition. *See* Pls.' Opp'n, Ex. A at 42–43. Dr. Lee does not recall exactly how long Plaintiff remained in the ICU. [1] *Id.* at 42–43.

*2 Much of the controversy in this case surrounds an "event" which allegedly occurred during Plaintiff's hospitalization. On September 25, 2007, an X-ray of Plaintiff's right knee revealed that her previously intact right knee prosthesis had subluxed (dislocated) by 3cm. Target's Mot. Summ. J., Ex. J. Plaintiff underwent emergency repair surgery on September 26, 2007, while her immune system was still compromised from the treatment of her other ailments. *Id.*, Ex. Q at 99–100. Despite the repair, Plaintiff subsequently developed an infection in her right knee requiring further treatment. Target's SUMF, ¶ 32. The infection persisted, which required doctors to remove the prosthesis and insert an antibiotic spacer. *Id.* at ¶ 33. Ultimately, Dr. Schoifet had to perform a "right knee arthrodesis," or fusion of Plaintiff's right knee. *Id.* at ¶ 34. Plaintiff's knee fusion has caused her significant pain, led to difficulty walking, and altered the range of activities in which she can participate. Dep. of Sandra Geiss at 90–94.

Although the subluxation was discovered on September 25, 2007, Plaintiff has no memory as to when or how it occurred. Target's Mot. Summ. J., Ex. T at 56–57. According to Plaintiff's expert, Dr. Gleimer, this subluxation occurred at some point while Plaintiff was hospitalized, but he cannot pinpoint a specific event, place or date. *Id.*, Ex. P–1 at 3. He does note, however, that the prosthetic is inherently stable and would not sublux on its own. *Id.* This confusion is enhanced due to a number of missing medical records. Specifically, Virtua cannot locate progress notes from August 29, 2007 to September 14, 2007, physician orders from September 4, 2007 to September 17, 2007, medical administration records from September 4, 2007 to September 19, 2007, and flow records from September 14, 2007, September 18, 2007 and October 3, 2007. Target's SUMF, ¶ 35. The Custodian of Records for Virtua, Jennfier Raio, attributes the loss of the records to human error. Virtua's Mot. Summ. J., Ex. D at 64–65.

On the basis of these events, Plaintiffs filed suit against Target on March 26, 2009 in the Superior Court of New Jersey, Burlington County. In the Complaint, Plaintiffs assert claims against Target for negligence and loss of consortium on behalf of Plaintiff Robert Geiss. Target was served on April 6, 2009. Within one month, Target properly moved the matter to this Court. On July 29, 2010, Target impleaded Virtua as a third party defendant in the case. In the Third Party Complaint, Target contends that Plaintiff's knee subluxation constitutes a superseding, intervening cause and that any injuries resulting therefrom are due solely to Virtua's negligence. Target seeks contribution and indemnification from Virtua for any damages for which Target may be liable to Plaintiffs in the underlying suit. Target's Third Party Compl., ¶ 11. Target also claims that it has been prejudiced by Virtua's failure to preserve all of Plaintiff's medical records and asserts a tort action for careless, negligent, and/or intentional spoliation of evidence, seeking contribution and/or indemnification as a remedy. *Id.* at 3–4.

*3 Both Virtua and Target now move for summary judgment. Target argues that Plaintiff's knee subluxation was neither actually nor proximately caused by Target's negligence. Target also contends that the expert opinion causally relating Plaintiff's fall at Target to her subsequent hospitalization should be barred as a net opinion. In its motion for judgment on the Third–Party Complaint, Virtua argues that neither party has adduced evidence supporting a prima facie case of negligence. Accordingly, Virtua asserts that there is no issue of material fact and that the hospital is entitled to judgment as a matter of law based on the current record.

II. STANDARD OF REVIEW

The court should grant a motion for summary judgment when the moving party "shows that there is no genuine dispute as to any material fact and that the movant is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(a). An issue is "material" to the dispute if it could alter the outcome, and a dispute of a material fact is "genuine" if "a reasonable jury could return a verdict for the non-moving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 249, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986); *Matsushida Elec. Indus. Co., Ltd. v. Zenith Radio*

Corp., 475 U.S. 574, 587, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986) ("Where the record taken as a whole could not lead a rational trier of fact to find for the non-moving party, there is no 'genuine issue for trial.' ") (quoting *First National Bank of Arizona v. Cities Service Co.*, 391 U.S. 253, 289, 88 S.Ct. 1575, 20 L.Ed.2d 569 (1968)). In deciding whether there is any genuine issue for trial, the court is not to weigh evidence or decide issues of fact. *Anderson*, 477 U.S. at 248. Because fact and credibility determinations are for the jury, the non-moving party's evidence is to be believed and ambiguities construed in her favor. *Id.* at 255; *Matsushida*, 475 U.S. at 587.

Although the movant bears the burden of demonstrating that there is no genuine issue of material fact, the non-movant likewise must present more than mere allegations or denials to successfully oppose summary judgment. *Anderson*, 477 U.S. at 256. The nonmoving party must at least present probative evidence from which jury might return a verdict in his favor. *Id.* at 257. The movant is entitled to summary judgment where the non-moving party fails to "make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986).

III. DISCUSSION & ANALYIS

Target's Third Party Complaint seeks contribution and indemnification from Virtua for any liability that Target may face in Plantiffs' underlying action. If Target's motion is granted, Virtua's motion for summary judgment would be rendered moot. Therefore, it is prudent for the Court to first address Target's motion for summary judgment.

A. Target's Motion for Partial Summary Judgment

Target moves for summary judgment based on Plaintiffs' alleged failure to establish causation. Target argues that its alleged negligence was neither the actual nor proximate cause of Plaintiff's knee subluxation and the complications resulting therefrom. Target further posits that Plaintiff's knee subluxation was a superseding intervening cause which severs the causal chain of liability. Target also seeks to bar Dr. Gleimer's conclusion that "all hospitalizations subsequent to July 25, 2007 related to Ms. Geiss' knee, back or related infection or problems were caused by the fall at Target." *See* Target's Mot. Summ. J. at 31. Target argues that Dr. Gleimer's statement is a "net opinion," which is unsubstantiated by objective evidence. *Id.* The Court will address these arguments in reverse order, beginning with Target's challenge to Plaintiffs' expert.

a. Sufficiency of Expert Testimony

***4** Target challenges Dr. Gleimer's conclusion that all hospitalizations subsequent to July 25, 2007 are causally related to Plaintiff's fall at Target, arguing that it is a "net opinion" that is unsupported by the factual record. Admissibility of expert testimony is governed by Rule 702, which was amended in 2000 to reflect the Supreme Court decision in *Daubert*. The Rule provides as follows:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. This rule requires a court to act as a "gatekeeper" to ensure that expert testimony is both relevant and reliable. *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir.2008). Rule 702 has a " 'liberal policy of admissibility.' " *Id*. (quoting *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 806 (3d Cir.1997)). The burden of showing expert testimony is admissible, once challenged, lies with the offering party. *See Kannankeril*, 128 F.3d at 807.

To be admissible, expert testimony must satisfy three requirements under Rule 702: 1) the witness must be an expert (i.e., must be qualified); 2) the expert must testify about matters requiring scientific, technical, or specialized knowledge (i.e., must be reliable); and 3) the expert's testimony must assist the trier of fact (i.e, must fit). *Id.* at 806 (citing *In re Paoli R.R. Yard PCB Litig. (Paoli II)*, 35 F.3d 717, 742 (3d Cir.1994)); *Elcock v. Kmart Corp.*, 233 F.3d 734, 741 (3d Cir.2000) (stating three requirements are qualifications, reliability, and fit). An expert is qualified if

he " 'possesses specialized expertise.' " *Pineda,* 520 F.3d at 244 (quoting *Schneider ex rel. Estate of Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003)). The qualification requirement is liberally construed. *Id.*

A reliable opinion is "based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation'; the expert must have 'good grounds' for his or her belief." *Paoli II,* 35 F.3d at 742 (quoting *Daubert,* 509 U.S. at 589). The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. *Daubert,* 509 U.S. at 595. In determining reliability, a court may look to several non-exhaustive factors, including:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non judicial uses to which the method has been put.

***5** *Elcock,* 233 F.3d at 745–46 (quoting *Paoli II,* 35 F.3d at 742 n. 8). Finally, an opinion fits a particular case (and thus helps the trier of fact) when there is a " 'connection between the scientific research or test result to be presented and particular disputed factual issues in the case.' " *Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000) (quoting *Paoli II,* 35 F.3d at 743). Fit is an issue of relevance and simply means that scientific validity of the method or principles applies to the issues at hand. *U.S. v. Ford,* 481 F.3d 215, 220 n. 6 (3d Cir.2007).

Target has not raised a proper *Daubert* challenge. Target does not challenge Dr. Gleimer's expertise, the reliability of his methodology, or the relevance of his opinion to this particular case. Target merely challenges the reliability of his conclusions. This is not the "inquiry envisioned by Rule 702." *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). As the Supreme Court cautioned, the overarching subject of a challenge under Rule 702 is "the scientific validity and thus the evidentiary relevance and reliability —of the principles that underlie a proposed submission." *Id.* Consequently, the Court's focus "must be solely on principles and methodology, not on the conclusions that they generate." *Id.*

Even construing Target's motion as a challenge to the reliability of Dr. Gleimer's methodology, Target has not raised any justification for barring his opinions. Target first argues that Dr. Gleimer "elected to disregard the medical evidence" and failed to explain how Plaintiff's presentation to the emergency room could have been caused by her fall. Target Mot. Summ. J. at 30. Target also finds significant that Dr. Gleimer cannot state exactly how and when the knee dislocation occurred, but attributes the dislocation to "some event/injury while in the hospital." *Id.* Target further contends that Dr. Gleimer failed to explicitly state that his opinions are based upon a reasonable degree of medical probability or certainty. *Id.* at 31. However, Dr. Gleimer did explain at length his reasons for reaching this conclusion. *See* Dr. Gleimer Dep. at 42–45. The balance of Target's arguments may be properly raised on cross-examination, not on a Rule 702 challenge. Therefore, the Court will deny Target's request to bar Dr. Gleimer's opinions.

b. Negligence

In order to establish negligence under the laws of New Jersey, a plaintiff must establish: (1) a duty of care owed to Plaintiff, (2) a breach of that duty, (3) actual and proximate causation, and (4) damages. *Jersey Cent. Power & Light Co. v. Melcar Utility Co.,* 212 N.J. 576, 594 (2013). Target only challenges Plaintiffs' ability to establish the third prong—actual and proximate causation.

i. Proximate Causation

Target argues that Plaintiff cannot establish that Target's negligence was the proximate cause of her knee subluxation. Target accords little weight to Dr. Gleimer's opinion that an "event" occurred during her hospitalization, but argues that even accepting this conclusion, "it is not foreseeable [that] any treatment for this alleged injury would cause a stable, intact knee prosthetic to dislocate, even if that treatment was negligently administered." Target's Mot. Summ. J. at 27.

Target also highlights that Plaintiff's own expert "does not state [that] plaintiff was receiving treatment for her back when the knee dislocation occurred, or that the dislocation of plaintiff's was a foreseeable consequence of such treatment." *Id.* However, none of these arguments justify summary judgment.

*6 Under well-established principles of tort law, "a tortfeasor is generally held answerable for the injuries which result in the ordinary course of events from his negligence and it is generally sufficient if his negligent conduct was a substantial factor in bringing about the injuries." *Rappaport v. Nichols,* 31 N.J. 188, 156 A.2d 1, 9 (N.J.1959). Therefore, to be considered a proximate cause, "conduct need only be a cause which sets off a foreseeable sequence of consequences, unbroken by any superseding cause, and which is a substantial factor in producing the particular injury." *Bendar v. Rosen,* 247 N.J.Super. 219, 588 A.2d 1264, 1269 (N.J.Super.Ct.App.Div.1991) (quoting *Scafidi,* 574 A.2d at 398). The New Jersey Supreme Court has been clear that "[p]roximate cause is a factual issue, to be resolved by the jury after appropriate instruction by the trial court." *Scafidi v. Seiler,* 119 N.J. 93, 574 A.2d 398, 402 (N.J.1990).

Contrary to Target's arguments, Plaintiffs have identified a triable issue of fact as to causation. First, Plaintiffs have offered ample evidence that Plaintiff's visit to the emergency room was spurred by severe back and knee pain. In her deposition, Plaintiff states that she had her husband call an ambulance "because of the excruciating pain she was experiencing in her knee and back." Pls.' SDMF, ¶ 3. Dr. Gleimer opines, and some of the emergency records indicate, that Plaintiff presented to the hospital with complaints of severe left leg pain, back pain, and ambulatory pain. *Id.,* Ex. F; Ex. P–2 at 1. The records also note that Plaintiff complained of "pain to lower back" and that Plaintiff "ambulate[d] slowly without assistance." *Id.* at 6–7.

Although, as Plaintiff concedes, the reasons for her actual admission remain less certain, Plaintiffs have also produced sufficient evidence on this point to survive summary judgment. Plaintiffs' expert, Dr. Gleimer, concluded that there were multiple reasons for Plaintiff's admission and observed that she was treated almost exclusively for her low back pain and sciatica. Pls.' Opp'n at 5(citing Gleimer Dep. at 44–45). Dr. Gleimer notes that these painkillers can also suppress respiration. *Id.* Dr. Gleimer also highlights that Virtua's Admission Record lists back pain as "one of the conditions chiefly responsible for Ms. Geiss' admission to Virtua." *Id.* (citing Gleimer Dep. at 45–46). Dr. Lee, the admitting doctor on the date in question, also testified that Plaintiff was admitted, at least in part, for "low back pain." *Id.* (citing Lee Dep. at 29). Thus, Plaintiffs have produced adequate evidence for a jury to find that Target's initial negligence was a proximate cause of her knee subluxation.

ii. Actual Causation

Target also argues that Plaintiff's fall was not the actual cause of her knee subluxation. Essentially, Target argues that because an x-ray confirmed that Plaintiff's prosthetic knee was in place after her initial fall and because Dr. Gleimer cannot state with certainty how or when the knee dislocation occurred, Target cannot be the actual cause of her subsequent injury. This argument fundamentally misconstrues the meaning of "actual cause." Actual cause serves as an "important corollary to the proximate cause rule." *See Dawson v. Bunker Hill Plaza Associates,* 289 N.J.Super. 309, 326, 673 A.2d 847 (App.Div.1996). In order to impose liability, a plaintiff must also establish that defendant's negligent conduct was "a substantial factor in bringing about harm to another." *Id.* An actor's conduct is not a substantial factor, "if [the injury] would have been sustained even if the actor had not been negligent.' " *Id.*

*7 Taking the evidence in the light most favorable to the non-moving party, Plaintiffs have established that Target's conduct was an actual cause of the knee subluxation. Target incorrectly focuses on whether the fall was the direct cause of Plaintiff's injury. However, the law is clear that Target can be liable, "even where there are 'other intervening causes which were foreseeable or were normal incidents of the risk created.' " *Camp v. Jiffy Lube No. 114,* 309 N.J.Super. 305, 309–10, 706 A.2d 1193 (App.Div.1998). Target has not provided any valid basis for summary judgment. Therefore, Target's motion for summary judgment is DENIED.

B. Virtua's Motion for Summary Judgment

Virtua has also moved for summary judgment on Target's Third–Party Complaint against the hospital. Virtua argues that "[n]o party has factually established a prima facie claim against Virtua for negligence." Virtua Mot. Summ. J. at 5. Virtua also contends that to the extent that

Target's claim against Virtua alleges medical malpractice, expert testimony is required to establish a deviation from accepted medical standards. *Id.* at 4, 706 A.2d 1193. Target responds with a number of arguments, none of which are presented with particular lucidity. Target first argues that it need not produce expert testimony because the "common knowledge" exception applies. Target then contends that Virtua's negligent spoliation of evidence entitles Target to an adverse inference. Target also raises the doctrine of "unclean hands" to thwart Virtua's motion for summary judgment. Finally, Target attempts to assert a claim for fraudulent concealment. The Court will address these arguments in turn.

a. Negligence

It is axiomatic that "the mere showing of an incident causing the injury sued upon is not alone sufficient to authorize the finding of an incident of negligence." *Long v. Landy,* 35 N.J. 44, 54, 171 A.2d 1 (1961). As a third-party plaintiff, Target bears the burden of demonstrating the existence of negligence. *See Buckelew v. Grossbard,* 87 N.J. 512, 435 A.2d 1150, 1157 (N.J.1981) ("We start with the basic proposition that ordinarily negligence must be proved and will never be presumed, that indeed there is a presumption against it, and that the burden of proving negligence is on the plaintiff"). Negligence may only be inferred from proven facts and circumstances and cannot be based on speculation or conjecture. *Long,* 35 N.J. at 54, 171 A.2d 1.

Target largely ignores these well-settled principles and attempts to survive summary judgment without providing any competent evidence of Virtua's negligence. Target argues that "the 'event' presumably occurred as a result of the carelessness, negligence, and/or gross negligence of Virtua." Target's Opp'n at 9. However, the law is clear that negligence "will never be presumed." *Buckelew,* 435 A.2d at 1157. Target first attempts to surmount this obstacle by invoking the "common knowledge" exception. According to Target, the common knowledge exception is applicable "where a lay person using ordinary understanding and experience is sufficient to determine a defendant's negligence without the benefit of expert testimony." Target's Opp'n (citing *Bender v. Walgreen Eastern Co. ., Inc.,* 399 N.J.Super. 584, 590, 945 A.2d 120 (N.J.Super.Ct.App.Div.2008)). Target previously raised this same exception in its opposition to Virtua's prior motion to dismiss in relation to the Affidavit of Merit requirement. The Court rejected its application then and will do so again.[2] *See* Doc. No. 30 at 7. Moreover, even if the Court did apply the common knowledge exception, it would not obviate Target's obligation to establish negligence. It merely alters the proofs upon which a plaintiff may rely to demonstrate a deviation from the standard of care.

*8 In addition to raising the common knowledge exception, Target makes two ill-fated attempts to establish a duty by Virtua. Target Mot. Summ. J. at 11. Target appears to argue that Virtua breached some duty to Target by failing to preserve evidence, which prejudiced Target. However, Target has not identified the source of such a duty. To the extent that Target relies on a common law duty to preserve evidence, Target has not established any of the required elements. The duty to preserve evidence only arises when there is pending or likely litigation between two parties, knowledge of this fact by the alleged spoliator, evidence relevant to the litigation, and the foreseeability that the opposing party would be prejudiced by the disposal of this evidence. *Cockerline v. Menendez,* 411 N.J.Super. 596, 620, 988 A.2d 575 (App.Div.2010). Target also argues that Virtua violated a statutory duty, imposed by N.J. 13:35–6.5, by failing to maintain complete and accurate records.[3] However, the statute does not give rise to a cause of action. *See Proske v. St. Barnabas Med. Ctr.,* 313 N.J.Super. 311, 318–19, 712 A.2d 1207 (App.Div.1998) (finding that N.J.S.A. 26:8–5 does not create a statutory cause of action and that "violation of the statute did not have a causal relation to the physical injury suffered"). Therefore, Target has not alleged any fact, much less provided competent evidence, of Virtua's negligence.[4]

b. Fraudulent Concealment of Evidence

Target also asserts a claim for fraudulent concealment of evidence against Virtua.[5] In order to prove this tort, a plaintiff must demonstrate that: (1) the defendant in the fraudulent concealment action had a legal obligation to disclose evidence in connection with *existing* or *pending* litigation, (2) the evidence was material to the litigation, (3) the plaintiff could not have reasonably obtained the evidence elsewhere, (4) the defendant *intentionally* withheld, altered, or destroyed evidence with purpose to disrupt litigation, (5) Plaintiff was damaged by having to rely on an incomplete record that did not contain the evidence defendant concealed. (emphasis added) *Rosenblit v. Zimmerman,* 166 N.J. 391, 406–07, 766 A.2d 749 (2001).

Target has not established these elements. Target has not provided any evidence that the missing records may have been material to this litigation. Target has not even established that Virtua intentionally withheld the missing entries. Even under the favorable standard of review on summary judgment, Target's claims cannot survive.

In the Third–Party Complaint, Target alleged claims for negligence and what this Court will construe as fraudulent concealment of evidence against Virtua. However, Target has failed to "make a showing sufficient to establish the existence of an element essential to [its] case." *Celotex*, 477 U.S. at 322. Therefore, the Court will grant Virtua's motion for summary judgment. [6]

IV. CONCLUSION

For the foregoing reasons, Target's Motion for Partial Summary Judgment is DENIED. Virtua's motion for summary judgment is GRANTED. An appropriate order shall issue today.

ORDER

*9 **THIS MATTER** having come before the Court on the motions of Virtua Memorial Hospital ("Virtua") and Target Corporation ("Target") for summary judgment, pursuant to Federal Rule of Civil Procedure 56, and the Court having considered the moving papers and attached documents, and the responses thereto, and for the reasons expressed in the Opinion issued this date;

IT IS HEREBY ORDERED that Target's motion for summary judgment is **DENIED.**

IT IS HEREBY FURTHER ORDERED that Virtua's motion for summary judgment on Target's Third Party Complaint is **GRANTED.**

All Citations

Not Reported in F.Supp.2d, 2013 WL 4675377

Footnotes

1 Plaintiff remained in the hospital until she was discharged on October 11, 2007. Target's SUMF, ¶ 24.

2 In the August 2, 2011 Opinion and Order, the Court stated: "Target has not demonstrated that its claim turns on common knowledge. Target alleges only that 'something' happened while Mrs. Geiss was at Virtua that caused her injuries. Target does not allege that an obvious error by Virtua or its employees caused Mrs. Geiss' injuries. Rather, Target acknowledges that it does not know the exact cause of her injuries. Because Mrs. Geiss received medical treatment, her injuries may have resulted from negligent medical care that requires expert testimony to prove."

3 Virtua notes that Target relies on the wrong statutory provision provision. According to Virtua, NJAC 13:35–6.5 is an administrative code and is not applicable to institutions. Virtua instead posits that NJSA 26:8–5 is the appropriate statutory provision mandating the maintenance of records.

4 Virtua also urges the Court to apply the doctrine of "unclean hands" and deny Virtua's motion for summary judgment. This doctrine "gives expression to the equitable principle that a court should not grant relief to one who is a wrongdoer with respect to the subject matter in the suit." *Faustin v. Lewis*, 85 N.J. 507, 427 A.2d 1105, 1107 (N.J.1981). As with every other argument in Target's opposition, Target has not demonstrated how this doctrine would be applicable. Although it is unfortunate that Virtua could not provide Plaintiff's complete medical record in discovery, Target has not provided any evidence of "wrongdoing with respect to the subject matter in the suit." Jennifer Raio testified that despite their best efforts in searching, her team had not been able to uncover the missing records. Jennifer Raio Dep., Target's Opp'n, Ex. D, 33–34. Moreover, Target has not produced any evidence or testimony linking Virtua's failure to maintain records to Plaintiff's actual injury.

5 The Third Party Complaint does not explicitly articulate a claim for fraudulent concealment, but it does contain allegations of spoliation of evidence. As Target states, spoliation of evidence claims are recognized as the tort of fraudulent concealment. *See Rosenblit v. Zimmerman*, 166 N.J. 391, 406, 766 A.2d 749 (2001).

6 Target also seeks an adverse inference jury instruction based on Virtua's alleged spoliation of evidence. Even if the Court were denying Virtua's motion, the Court would not be inclined to address jury instruction requests on a motion for summary judgment.

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EXHIBIT 20

2017 WL 1352860
Only the Westlaw citation is currently available.
United States District Court,
E.D. Louisiana.

IN RE: XARELTO (RIVAROXABAN) PRODUCTS LIABILITY LITIGATION
This Document Relates to: All Cases

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ORDER & REASONS

SECTION L

ELDON E. FALLON, UNITED STATES DISTRICT JUDGE

*1 Before the Court are several motions to exclude certain areas of anticipated testimony of various expert witnesses for the Boudreaux and Orr bellwether trials. Having considered the parties arguments and the applicable law, the Court now issues this order and reasons.

I. *DAUBERT* LEGAL STANDARD

Rule 702 of the Federal Rules of Evidence governs the admissibility of expert testimony. Rule 702 is in effect a codification of the United States Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993). In *Daubert*, the Supreme Court held that trial courts should serve as gatekeepers for expert testimony and should not admit such testimony without first determining that the testimony is both "reliable" and "relevant." *Id.* at 589.

The trial court is the gatekeeper of scientific evidence. *Daubert*, 509 U.S. at 596. It has a special obligation to ensure that any and all expert testimony meets these standards. *Id.* Accordingly, it must make a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and whether the reasoning or methodology can be properly applied to the facts in issue. *Id.* at 592–93. In making this assessment, the trial court need not take the expert's word for it. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147 (1997). Instead, when expert testimony is speculative or lacks scientific validity, trial courts are encouraged to exclude it. *Moore v. Ashland Chem., Inc.*, 151 F.3d 269, 279 (5th Cir. 1998).

In satisfying its "gatekeeper" duty, the Court will look at the qualifications of the experts and the methodology used in reaching their opinions and will not attempt to determine the accuracy of the conclusion reached by the expert. The validity or correctness of the conclusions is a determination to be made by the fact finder after the *Daubert* analysis.

Scientific testimony is reliable only if "the reasoning or methodology underlying the testimony is scientifically valid," meaning that such testimony is based on recognized methodology and supported by appropriate validation based on what is known. *Daubert*, 509 U.S. at 592–93. In *Daubert*, the Supreme Court set forth a non-exclusive list of factors to consider in determining the scientific reliability of expert testimony. *Id.* at 593–95. In the context of the present case, these factors are: (1) whether the theory has been tested; (2) whether the theory has been subject to peer review and publication; (3) the known or potential rate of error; (4) whether standards and controls exist and have been maintained with respect to the technique; and (5) the general acceptance of the methodology in the scientific community. *Id.* Whether some or all of these factors apply in a particular case depends on the facts, the expert's particular expertise, and the subject of his testimony. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 138 (1999).

In addition to the five factors laid out in *Daubert*, a trial court may consider additional factors to assess the scientific reliability of expert testimony. *Black v. Food Lion, Inc.*, 171 F.3d 308, 312 (5th Cir. 1999). These factors may include: (1) whether the expert's opinion is based on incomplete or inaccurate data; (2) whether the expert has identified the specific mechanism by which the drug supposedly causes the alleged disease; (3) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion; (4) whether the expert has adequately accounted for alternative explanations; and (5) whether the expert proposes to testify about matters growing directly out of research he

or she has conducted independent of the litigation. *See, e.g., id.* at 313; *Moore v. Ashland Chem., Inc.*, 151 F.3d 269, 278–79 (5th Cir. 1998); *Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1114 (5th Cir. 1991); *Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 678 (W.D. Tex. 2002). Scientific testimony is relevant only if the expert's reasoning or methodology can be properly applied to the facts at issue, meaning there is an appropriate fit between the scientific testimony and the specific facts of the case. *Daubert*, 509 U.S. at 593. Scientific evidence is irrelevant, however, when there is too great an analytical gap between the data and the opinion proffered. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

*2 The party seeking to introduce the expert testimony bears the burden of demonstrating that the testimony is both relevant and reliable. *Moore*, 151 F.3d at 275–76. The requirement of reliability does not strictly bind an expert within the proffered field of expertise; an expert may also testify concerning related applications of his or her background. *Slatten, LLC v. Royal Caribbean Cruises Ltd.*, No. 13-673, 2014 WL 5393341, at *2 (E.D. La. Oct. 23, 2014) (citing *Wheeler v. John Deere Co.*, 935 F. 2d 1090, 1100 (10th Cir. 1991)). The focus is not on the result or conclusion, but on the methodology. *Moore*, 151 F.3d at 275–76. The proponent need not prove that the expert's testimony is correct, but must prove by a preponderance of the evidence that the expert's methodology was proper. *Id.* Both the Plaintiffs and Defendants have various experts in this case. The Court will address each of the motions in turn.

A. Defendants' Motion to Exclude Certain Opinions of Dr. Laura Plunkett

Before the Court is Defendant's Motion to Exclude Certain opinions of Dr. Laura M. Plunkett, Ph.D., DABT (R. Doc. 5108). Defendants seek to limit Dr. Plunkett's testimony regarding Xarelto labeling and the state of mind or knowledge of both Defendants and the FDA. Plaintiffs disagree, arguing that Dr. Plunkett's testimony is well within her expertise and pointing out that most courts which have considered her qualifications and methodology have found her "eminently qualified to testify about drug pharmacology, general causation, regulatory matters and the adequacy of labels for both prescription and non-prescription drugs." Plaintiffs contend that in arguing that Dr. Plunkett is not qualified in regulatory or labeling, Defendants are arguing that she is not qualified to do exactly what she does when consulting for pharmaceutical companies.

Dr. Plunkett is a pharmacologist and toxicologist who has substantial experience as an expert witness. She is a Diplomate of the American Board of Toxicology and a registered patent agent. She is neither a medical doctor nor a regulatory agent for the FDA, but has extensive experience consulting and advising as to regulatory matters, including label content. The Defendants do not dispute Dr. Plunkett's qualifications, and this Court finds she is well-qualified by her experience and education.

The Court further finds that Dr. Plunkett's opinions are based on her review of Defendants' and the FDA's statements and documents, as well as medical journals and reports. Defendants' arguments go to the witness's conclusions, not her methodology or qualifications, and accordingly may be dealt with by cross-examination at trial.

Accordingly, Defendants' Motion (R. Doc. 5108) is **DENIED**.

B. Defendants' Motion to Exclude Certain Opinions of Dr. David Kessler

Before the Court is Defendants' Motion to exclude portions of Dr. David Kessler's expert report that lack a reliable foundation and that are inappropriate testimony for an expert witness. (R. Doc. 5111). Plaintiffs oppose the Motion, arguing that Defendants take pieces of Dr. Kessler's opinion out of context in making their failing arguments. Plaintiffs further contend Dr. Kessler is uniquely qualified to offer opinions on the conduct of pharmaceutical companies.

Dr. David Kessler, M.D., is a medical doctor, the former Commissioner of the Food and Drug Administration, a professor of food and drug law, and an advisor to pharmaceutical companies. He has testified before Congress on multiple occasions and has published numerous articles in legal, medical, and scientific journals on the federal regulation of drugs and medical devises as well as the intersection of federal regulation and state law. Currently, Dr. Kessler is a senior advisor to a global private equity firm that owns pharmaceutical and biomedical companies and serves on the boards of two pharmaceutical companies. He advises corporates on the proper standard of care under both state and federal law.

*3 The Court finds Dr. Kessler is well qualified by virtue of his education and prior positions to render expert opinions. He bases his opinions on medical literature, federal regulations, and his experience. He uses appropriate methodology in forming his opinions. The objections Defendants argue in their motion are better reserved for cross-examination at trial. Accordingly, Defendants' Motion (R. Doc. 5111) is **DENIED**.

C. Defendants' Motion to Exclude Certain Opinions of Dr. Suzanne Parisian

Before the Court is Defendants' Motion to exclude certain portions of Dr. Suzanne Parisian's expert report. (R. Doc. 5112). Specifically, they argue her recitation of Xarelto's regulatory history is not proper expert witness testimony, and that she is unqualified and uses poor methodology in giving her opinions on medical or regulatory causation, foreign regulatory issues, and what information is important to patients or doctors. Plaintiffs oppose the motion, arguing Dr. Parisian is highly qualified and is one of the few people who specializes in the complexities of FDA regulation. They aver Dr. Parisian will assist the jury in understanding the regulatory requirements applicable to pharmaceutical manufacturers and drug labeling within the context of the FDA.

The Court finds that Dr. Parisian is qualified by virtue of education and experience and she uses sound methodology in reaching her conclusions. The thrust of the Defendants' objections seems to be that they are concerned the witness may assume an advocate role at trial. If Dr. Parisian assumes an advocate role at trial, the Court will address it at that time. For the time being, however, Defendants' Motion (R. Doc. 5112) is **DENIED**.

D. Defendants' Motions Regarding Unapproved Dosage and Monitoring Regimens and the 20-second PT cutoff guideline

Before the Court are Defendants' Motions to Exclude Expert Opinions and Testimony Regarding Unapproved Dosage and Monitoring Regimens (R. Doc. 5113) and to Preclude Opinions and Testimony Regarding Plaintiffs' Experts' 20-second PT cutoff guideline. (R. Doc. 5114).

1. Dosage and Monitoring Regimens

Defendants aver that Plaintiffs expert witnesses opine that patients' risk of bleeding could be reduced if doctors monitored the concentration or anticoagulant effect of Xarelto, and if the FDA-approved dosages were changed. In approving Xarelto, the FDA approved a fixed-dose regimen of 20 milligrams once a day. Plaintiffs oppose Defendants' motion, arguing that the motion is procedurally improper. FRE 702 is meant to exclude or allow particular witnesses based on their qualifications and methodology; it is not meant to exclude or allow entire issues. Daubert motions are meant to address methodology and qualifications; this motion does not do so. The Defendants do not question any particular expert's specialized knowledge or methodology, preventing the court from meaningfully evaluating the issues and experts. Further, Plaintiffs contend that Defendants take quotes and opinions entirely out of context, making Plaintiffs' experts appear to say or testify to something different than that to which they are actually testifying.

2. 20-second PT cutoff guideline

Several of Plaintiffs' Expert Witnesses opine that if physicians monitored the concentration of anticoagulation effect of Xarelto in their patients—particularly by using prothrombin time ("PT") using a Neoplastin reagent—bleeding risk would be reduced. PT is a non-specific method to measure the amount of time it takes a person on an anticoagulant to clot. Defendants seek to preclude any expert testimony regarding the 20-second PT cutoff discussed by several of Plaintiffs' experts. They construe Plaintiffs' argument as: any patient with a PT level higher than a certain point should be switched to an alternate anticoagulant or be prescribed a lower, non-FDA approved dose of Xarelto. This argument, Defendants aver, is not reliable and does not fit the facts of the Orr and Boudreaux bellwether cases and is therefore not relevant to the litigation.

*4 Plaintiffs contend that the PT tests are factually significant to this case. They aver that the Bellwether Plaintiffs must have had a high Neoplastin PT result because they had a significant bleeding episode. Relying on FDA and Defendant-supported data, a high Neoplastin PT result and a bleeding episode are

correlated. The possible use of a Neoplastin PT test to these Bellwether Plaintiffs should not be disputed. Further, Plaintiffs contend that Dr. Rinder relied on peer-reviewed literature to compare PT values. His report was neither late nor unscientific, and he produced the chart he used in his determination. Plaintiffs argue Dr. Rinder never claims to be converting the PT numbers, just making an indirect comparison and approximation based on the chart. His methods, Plaintiffs contend, are sound.

3. Analysis

The Court finds that the opinions Defendants seek to exclude go to the crux of Plaintiffs' theory of the case. Dosing and monitoring (including the 20-second PT cutoff) are relevant to Plaintiffs' theory that Xarelto was defectively designed and its label lacked relevant information or directions regarding its safe use. Because of Xarelto's short half-life and the variability in patients, some patients will retain more Xarelto in their system and will be subject to a greater bleeding risk. Xarelto's dosing scheme and the availability of monitoring bear on the individual risk to each plaintiff taking Xarelto. Plaintiffs contend that proper usage requires testing or monitoring to ascertain the appropriate dosage. They argue that this was known or should have been known to Defendants and the label should contain information and instructions or directions as to proper use. Plaintiffs point to various journals and studies supporting their position. Without judging the accuracy of this conclusion, the methodology supporting the Plaintiffs' argument is appropriate. Defendants' quarrel is with the witnesses' conclusions and not their methodology. Accordingly, Defendants' Motions (R. Docs. 5113, 5114) are **DENIED**.

E. Plaintiffs' Motion to Exclude Certain Opinions of Dr. James Reiffel

Before the Court is Plaintiffs' Motion to Preclude Dr. James A. Reiffel, M.D., from testifying regarding attorney advertising and earlier cancer detection from anticoagulant-elated bleeds. (R. Doc. 5116). Defendants oppose, arguing his testimony is reliable and relevant. Further, they contend that limiting their ability to make arguments about attorney advertising would be prejudicial because Plaintiffs plan to discuss Defendants' Xarelto advertisements. Further, the statements regarding early detection of diseases such as cancer are relevant and reliable as part of the entire risk-benefit analysis of Xarelto. The entire analysis, they aver, must be weighed by a jury when ascertaining whether or not Xarelto was defectively designed.

This Court finds that Dr. Reiffel's testimony regarding the effect of attorney advertising is not relevant or reliable and is therefore excluded. However, such testimony may be offered as rebuttal testimony if the issue is raised on direct examination at trial. For example, if there is evidence that the patient in question avoided taking Xarelto or abruptly stopped taking Xarelto due to attorney advertising, then this ruling may have to be modified.

This Court also finds Dr. Reiffel's testimony regarding early cancer detection to be irrelevant in this case, as cancer was not an issue for either Plaintiff. Further, there is no evidence that Xarelto is routinely prescribed to screen for cancer. Accordingly, such testimony is also excluded. If this becomes an issue during the trial, then this ruling will be modified.

For the aforementioned reasons, **IT IS ORDERED** that Plaintiffs' Motion (R. Doc. 5116) is **GRANTED**.

F. Defendants' Motion to Exclude Certain Opinions of Dr. Nathaniel Winstead

*5 Before the Court is Defendants' Motion to exclude part of Dr. Nathaniel Winstead's expert report, specifically his opinion that Xarelto can cause internal bleeding absent any underlying pathology because his methodology does not meet the requirement under *Daubert* and its progeny. (R. Doc. 5120). Dr. Winstead is a case-specific expert in the *Boudreaux* bellwether case. Plaintiffs oppose the motion, arguing that Dr. Winstead is qualified to provide expert testimony regarding Xarelto's ability to cause internal bleeding through "systemic toxicity," and point out that Dr. Winstead's main opinion, which Defendants don't oppose, is that Xarelto is the most probable cause of Plaintiff Boudreaux's gastrointestinal bleed. Further, Plaintiffs argue that rather than a mere hypothesis, Dr. Winstead's opinion is supported by his clinical experience, peer-reviewed studies, and other sources including Xarelto's label.

Dr. Nathaniel Winstead, MD, is a general gastroenterologist and hepatologist with clinical experience with Warfarin, and is double-board-certified in gastroenterology and internal medicine. In researching for

and writing his expert report, Dr. Winstead attests that he used the same methods he uses to evaluate and treat his patients. From 2008-2013, Dr. Winstead was the Director of Gastroenterology Research and the Medical Director of the Inflammatory Bowel Disease Center at Ochsner. He was the principal investigator or sub-investigator in multiple clinical trials for various drug manufacturers, including Defendant Janssen. As a medical doctor, Dr. Winstead sees approximately 100-200 GI bleeds a year and has regularly concluded that certain bleeds are a result of anticoagulants themselves, including through systemic toxicity. In preparing for this case, Dr. Winstead reviewed Plaintiff Boudreaux's medical records, depositions of other witnesses, various iterations of Xarelto's label, and numerous Xarelto studies.

The Court finds Dr. Winstead is qualified by virtue of his training and experience. He reaches his conclusion that NOACs, and specifically Xarelto, can cause bleeding without underlying pathology through his experience, the presence of the drug in Plaintiff's stool, peer reviewed literature, and Xarelto's label. Defendants may cross-examine Dr. Winstead on these issues at trial in an attempt to establish the frailty of the basis of his conclusions, but excluding them at this time is inappropriate.

For the aforementioned reasons, **IT IS ORDERED** that Defendants' Motion (R. Doc. 5120) is **DENIED**.

G. Plaintiffs' Motion to Preclude Speculative Testimony About Potential Outcomes from Other Anticoagulants

Before the Court is Plaintiffs' Motion to Preclude Speculative Testimony About Potential Outcomes from Other Anticoagulants which asks the Court to prevent Drs. Smith, Piazza, and Branch from testifying about what might have happened to the bellwether Plaintiffs if they had taken a different anticoagulant. (R. Doc. 5121). Defendants contend that Plaintiffs misconstrue their experts' testimony, arguing that their opinions are relevant to rebut Plaintiffs' claim that Xarelto is not as reliable as other drugs and that there is a safer alternative. To not allow this testimony, Defendants contend, would be prejudicial to their case and their ability to defend themselves against Plaintiffs' theories.

One of Plaintiffs' theories in this case is that Xarelto was defectively designed. Under the Louisiana Products Liability Act, this requires showing that a safer alternative design existed. The evidence presented here by Defendants' experts, Drs. Smith, Piazza, and Branch, attempts to rebut the claim of a safer alternative design and accordingly is admissible on rebuttal of Plaintiffs' defective design theory. The Doctors' opinions are based on their experience and training, are relevant, and are based on proper methodology. At trial, Plaintiffs may cross-examine these witnesses as to the validity of their conclusions, but excluding their testimony at this stage would be improper. The Court, however, may revisit this issue at trial if the evidence so warrants.

***6** For the aforementioned reasons, **IT IS ORDERED** that Plaintiffs' Motion (R. Doc. 5121) is **DENIED**.

H. Plaintiffs' Motion to Exclude Certain Opinions of Dr. J. Michael Gaziano

Before the Court is Plaintiffs' Motion to preclude certain testimony from Dr. J. Michael Gaziano, MD, MPH, regarding the adequacy of Xarelto's label, Xarelto's dosing scheme, and the Time in Therapeutic Range (TTR) for warfarin as compared to Xarelto. (R. Doc. 5127). Defendants disagree, arguing that Plaintiffs mischaracterize Dr. Gaziano's opinions and aver that he is more than qualified to offer this testimony based on his extensive experience, training as a cardiologist and epidemiologist, his clinical trial experience, his research, and his review of medical literature on Xarelto and other anticoagulants.

Dr. J. Michael Gaziano, MD, MPH, has been a physician for 30 years. He received his MD from Yale and his MPH with a concentration in cardio-epidemiology from Harvard. He is a cardiologist in Boston where he teaches and sees patients including those who require anticoagulant therapy. Dr. Gaziano is a professor at Harvard Medical School and an adjunct professor at Boston University Medical School, and is board certified in cardiovascular disease. Throughout his career he has participated in and directed clinical trials and has also published various books and articles focusing on cardiology.

The Court finds Dr. Gaziano is well qualified by his education and experience, and that his opinions are based on his experience and his review of test data and literature. Dr. Gaziano's opinions are based on proper methodology and are relevant to the issues in dispute in this case. Further, the thrust of Plaintiffs' concerns lie

in Dr. Gaziano's conclusions, not his methodology or qualifications. Accordingly, Plaintiffs concerns are better dealt with on cross-examination at trial.

For the aforementioned reasons, **IT IS ORDERED** that Plaintiffs' Motion (R. Doc. 5127) is **DENIED**.

I. Plaintiffs' Motion to Preclude Speculative Testimony About Potential Outcomes from Other Anticoagulants

Before the Court is Plaintiffs' second Motion to Preclude Speculative Testimony About Potential Outcomes from Other Anticoagulants, which asks the Court to prevent Drs. Boniol, Johnson, Kahn, Eiswirth, and Peacock from testifying about what might have happened to the bellwether Plaintiffs if they had taken a different anticoagulant. (R. Doc. 5399). They argue these opinions were not subject to peer review or tested, are without standards controlling their opinion, and are not generally accepted within the scientific community. They also argue such opinions are irrelevant and run a high risk of undue prejudice. Adopting their opposition to the first motion to exclude speculative testimony, Defendants contend that Plaintiffs misconstrue their experts' testimony, arguing that their opinions are relevant to rebut Plaintiffs' claim that Xarelto is not as reliable as other drugs and that there is a safer alternative. To not allow this testimony, Defendants contend, would be prejudicial to their case and their ability to defend themselves against Plaintiffs' theories. Defendants further argue that Plaintiffs own expert witnesses agree that they cannot rule out the possibility of a bleeding event on another anticoagulant. Further, Defendants contend that all of the doctors base their opinions on their education, training and expertise and on extensive review of relevant studies, literature, and medical records.

*7 One of Plaintiffs' arguments is that there is a safer alternative to Xarelto. The testimony of these expert witnesses seeks to rebut that theory. Further, the testimony goes toward Defendants' theory that Xarelto was an appropriate drug for Plaintiffs to take. This Court finds the testimony is proper as the experts are well-qualified and their testimony is relevant and based on proper methodology. Accordingly, Plaintiffs' Motion (R. Doc. 5399) is **DENIED**.

J. Plaintiffs' Motion to Exclude Certain Opinions of Drs. Scott Boniol and William Franklin Peacock IV

Before the Court is Plaintiffs' Motion to exclude the section of Dr. Scott Boniol's and Dr. William Franklin Peacock IV's expert reports that opine on the earlier detection of cancer and other diseases due to anticoagulant-related bleeding events. (R. Doc. 5401). Defendants oppose the motion, arguing the statements regarding early detection of diseases such as cancer are relevant and reliable as part of the entire risk-benefit analysis of Xarelto. The entire analysis, they aver, must be weighed by a jury when ascertaining whether or not Xarelto was defectively designed.

Dr. Scott Boniol, MD, is a hematologist and oncologist. Dr. William Franklin Peacock IV, MD, FACEP, is a board-certified emergency medicine physician and a fellow of the American Colleges of Emergency Physicians and Cardiology. Plaintiffs do not dispute either doctor's expert credentials, and the Court finds they are qualified by virtue of their education and experience to offer expert testimony.

The Court finds the testimony of Drs. Boniol and Peacock regarding early cancer detection to be irrelevant in this case, as cancer was not an issue for either Plaintiff. Further, there is no evidence that Xarelto is routinely prescribed to screen for cancer. Accordingly, such testimony is excluded. If this becomes an issue during the trial, then this ruling will be modified). Accordingly, Plaintiffs' motion (R. Doc. 5401) is **GRANTED**.

K. Plaintiffs' Motion to Exclude Certain Opinions of Dr. Scott Boniol

Before the Court is Plaintiffs' Motion to exclude the section of Dr. Scott Boniol's expert report that gives his opinion about the effects of attorney advertising because they are subjective, unscientific, unreliable, and unduly prejudicial. (R. Doc. 5404). Defendants oppose, arguing his testimony is reliable and relevant. Further, they contend that limiting their ability to make arguments about attorney advertising would be prejudicial because Plaintiffs plan to discuss Defendants' Xarelto advertisements.

Dr. Scott Boniol, MD, is a hematologist and oncologist. Plaintiffs do not dispute his expert credentials, and the Court finds he is qualified by nature of his education and experience to offer expert testimony. Further, his opinions regarding Xarelto are based on experience, data, and on medical journals. However, the Court finds Dr. Boniol's

commentary on attorney advertising and the effect of that advertising on patients is argumentative and are excluded under F.R.E. 401 and 403. Dr. Boniol may discuss the danger to patients who prematurely stop taking Xarelto, but may not relate that danger to attorney advertising. However, testimony regarding attorney advertising may be offered as rebuttal testimony if the issue is raised on direct examination at trial. If there is evidence that the patient in question avoided taking Xarelto or abruptly stopped taking Xarelto due to attorney advertising, then this ruling may have to be modified.

*8 Consistent with the aforementioned reasons, **IT IS ORDERED** that Plaintiffs' Motion (R. Doc. 5404) is **DENIED IN PART** and **GRANTED IN PART**.

II. CONCLUSION

For the aforementioned reasons, **IT IS ORDERED** that Defendants' Motion to exclude certain opinions of Dr. Laura Plunkett (R. Doc. 5108) is **DENIED**.

IT IS FURTHER ORDERED that Defendants' Motion to exclude certain opinions of Dr. David Kessler (R. Doc. 5111) is **DENIED**.

IT IS FURTHER ORDERED that Defendants' Motion to exclude certain opinions of Dr. Suzanne Parisian (R. Doc. 5112) is **DENIED**.

IT IS FURTHER ORDERED that Defendants' Motion to exclude expert opinions and testimony regarding unapproved dosage and monitoring regimens (R. Doc. 5113) is **DENIED**.

IT IS FURTHER ORDERED that Defendants' Motion to preclude opinions and testimony regarding Plaintiffs' experts' 20-second PT cutoff guideline (R. Doc. 5114) is **DENIED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to exclude certain opinions of Dr. James Reiffel (R. Doc. 5116) is **DENIED**.

IT IS FURTHER ORDERED that Defendants' Motion to exclude certain opinions of Dr. Nathaniel Winstead (R. Doc. 5120) is **DENIED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to preclude speculative testimony about potential outcomes from other anticoagulants (R. Doc. 5121) is **DENIED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to exclude certain opinions of Dr. J. Michael Gaziano (R. Doc. 5127) is **DENIED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to preclude speculative testimony about potential outcomes from other anticoagulants (R. Doc. 5399) is **DENIED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to exclude certain opinions of Drs. Scott Boniol and William Franklin Peacock IV (R. Doc. 5401) is **GRANTED**.

IT IS FURTHER ORDERED that Plaintiffs' Motion to exclude certain opinions of Dr. Scott Boniol (R. Doc. 5404) is **GRANTED IN PART** and **DENIED IN PART**.

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EXHIBIT 21

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United States District Court,
D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.
Bernadette Glynn and Richard Glynn, Plaintiffs,
v.
Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.
|
April 10, 2013.

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OPINION

PISANO, District Judge.

***1** Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") bring this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), which manufactures Fosamax, a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs[1]") and that it caused Plaintiff Mrs. Glynn ("Mrs.Glynn")'s femur fracture. Presently before the Court is Defendant's Omnibus *Daubert* Motion to exclude the expert testimony of Dr. Charles N. Cornell ("Dr.Cornell"), Dr. Michael J. Klein ("Dr.Klein"), Dr. David Madigan ("Dr.Madigan"), and Dr. Cheryl Blume ("Dr.Blume") as well as a motion to exclude the causation testimony of the treating physicians—Dr. Robert Busch ("Dr.Busch"), Dr. Robert Lindsay ("Dr.Lindsay"), Dr. Frederick Fletcher ("Dr.Fletcher"), and Dr. Britton Limes ("Dr.Limes") [docket # 28]. This Court heard oral argument on February 21, 2013 and April 2, 2013. For the reasons outlined below, the Motion is denied as to Drs. Cornell, Klein, Madigan, and Blume. The treating physicians' causation testimony will not be excluded if their opinions are based on their treatment and care of Mrs. Glynn.

I. DISCUSSION

Federal Rule of Evidence 702 provides that a witness

> qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

This Rule requires the proponent of expert testimony to show the "requisite 'qualifications, reliability, and fit' " or in other words, that "(1) the witness is qualified as an expert in a particular field; (2) the methodology applied by the witness is sufficiently reliable; and (3) the witness's testimony 'fits' the facts of the case in dispute—that is, the proffered testimony would assist the trier of fact." *Jones v. Synthes USA Sales, LLC,* 2010 WL 3311840, *4 (D.N.J. Aug.19, 2010); *see also McNamara v. Kmart Corp.,* 380 Fed. Appx. 148, 151 (3d Cir.2010); *Meadows v. Anchor Longwall & Rebuild, Inc.,* 306 Fed. Appx. 781, 788 (3d Cir.2009); *Pineda v. Ford Motor Co.,* 520 F.3d 237, 244 (3d Cir.2008); *Schneider ex rel. Estate of Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003).

First, the expert must be qualified; this requirement is interpreted liberally and "a broad range of knowledge, skills, and training qualify an expert as such." *In re Paoli R.R. Yard PCB Litigation,* 35 F.3d 717, 741 (3d Cir.1994).

*2 Second, "an expert's testimony is admissible so long as the process or technique the expert used in formulating the opinion is reliable." *Id.* at 742. An expert's opinion is reliable if it is "based on 'good grounds,' i.e., if it is based on the methods and procedures of science." *Id.* at 744. This inquiry requires a court to examine the "scientific validity and thus the evidentiary relevance and reliability [ ] of the principles that underlie a proposed submission" and to focus "solely on principles and methodology, not on the conclusions ... [the expert] generate[s]." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–95, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). In *Daubert*, the Supreme Court outlined several factors that a court may take into consideration in determining reliability, including whether the hypothesis can be tested, whether the methodology "has been subjected to peer review and publication," the methodology's rate of error, "the existence and maintenance of standards controlling the technique's operation," and whether there is general acceptance in the scientific community. *Id.* at 593–94. The proponent of the expert testimony must demonstrate that the opinions are reliable by a preponderance of the evidence. *In re Paoli*, 35 F.3d at 744.

Third, expert testimony "must fit the issues in the case" or in other words, "be relevant for the purposes of the case and must assist the trier of fact." *Schneider*, 320 F.3d at 404. The Court must determine "whether [the] expert testimony proffered ... is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." *United States v. Schiff*, 602 F.3d 152, 173 (3d Cir.2010). This standard "is not that high" but "higher than bare relevance." *In re Paoli*, 35 F.3d at 745.

The Court's role, at a *Daubert* hearing, is to act "as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury." *Schneider*, 320 F.3d at 404. In keeping with its gatekeeping role, this Court will apply the *Daubert* analysis to each expert.

A. Dr. Cornell

Plaintiffs offer Dr. Cornell, an orthopedist, as an expert in causation, to establish that Fosamax causes AFFs and Mrs. Glynn's Fosamax use caused her AFF.

1. Dr. Cornell Is Qualified as an Expert

Dr. Cornell is currently a Professor of Clinical Orthopedic Surgery at Weill Cornell College of Medicine and has been the Richard Laskin Chair in Orthopedic Surgery since 2011 [docket # 102, Ex. 8, Dr. Cornell's Report ("Cornell Report") at 2]. In addition, Dr. Cornell is an attending orthopedic surgeon at the Hospital for Special Surgery in New York City and currently serves as the hospital's Director of the Department of Orthopedic Surgery. *Id.* He is a "specialist in orthopedic trauma ... and metabolic bone disease," which includes osteoporosis and osteopenia [docket # 102, Ex. 10, Dr. Cornell's Deposition ("Cornell Dep.") at 69:13–16; 71:14–17]. About 80% of all the fractures Dr. Cornell treats surgically are fractures "as a consequence of osteoporosis or osteopenia." *Id.* at 72:6–21. He has treated two patients with atypical fractures related to bisphosphonate use. Cornell Report at 3. Moreover, he has "participated in a study to determine a management strategy for the treatment of symptomatic bisphosphonate-associated incomplete atypical femoral fractures, which was peer reviewed and published in the Hospital for Special Surgery Journal." *Id.* Although Defendant argues that Dr. Cornell is not qualified because he is not trained in epidemiology and is unfamiliar with "the most basic epidemiological terms and concepts" (Db13[2]), Dr. Cornell does not have to possess a particular subspecialty—epidemiology—to testify as an expert. *See Schneider*, 320 F.3d at 406–07 (determining that testimony was improperly excluded because an individual "was not an expert in the sub-specialty about which he opined"); *Holbrook v. Lykes Bros. S.S. Co., Inc.*, 80 F.3d 777, 783 (3d Cir.1996) (declaring that the lower court erred by requiring the expert to have a particular specialization and "exact background"); *see also Keller v. Feasterville Family Health Care Ctr.*, 557 F.Supp.2d 671, 675 (E.D.Pa.2008) (recognizing that expert testimony cannot be excluded because "the expert is without the appropriate specialization" and that "[a] certain degree of background is not required"). Because Dr. Cornell has the academic background and professional experience with osteoporosis, osteopenia, and fractures associated with those diseases, he is qualified to testify as an expert in this case. *See Schneider*, 320 F.3d at 407.

2. Dr. Cornell's Methodology Is Sufficiently Reliable

*3 Dr. Cornell formed his opinion using the Bradford Hill criteria, which are "nine factors widely used in the scientific community to assess general causation." *Gannon v. United Sates*, 292 Fed. Appx. 170, 173 (3d Cir.2008);

Cornell Dep. at 329:5–8. General causation is when "an observed association between a chemical and a disease is causal." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 592 (D.N.J.2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir.2003). The nine Bradford Hill factors are: "1. Temporal Relationship, 2. Strength of the association, 3. Dose-response relationship, 4. Replication of the findings, 5. Biological plausibility (coherence with existing knowledge), 6. Consideration of alternative explanations, 7. Cessation of exposure, 8. Specificity of the association, and 9. Consistency with other knowledge." FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 599–600 (3d ed.2011), *available at* http://www.fjc.gov/public/pd f.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf; *see also Gannon*, 292 Fed. Appx. at 173 n. 1; *In re Avandia Mktg., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, *3 (E.D.Pa. Jan.4, 2011); *Magistrini*, 180 F.Supp.2d at 592–93. "[O]ne or more of the factors may be absent even where a causal relationship exists and ... no factor is a sine qua non of causation. *Magistrini*, 180 F.Supp.2d at 593 n. 9.

Dr. Cornell used the Bradford Hill criteria to form an opinion on whether Fosamax causes AFFs. Cornell Dep. at 331:4–8; Cornell Report at 4. In applying the nine Bradford Hill factors, he reviewed Plaintiff's medical records from 1996 to present, the office notes and depositions of her treating physicians, and "past and current medical literature on the topics of osteopenia, osteoporosis and their prevention and treatment with bisphosphonate drugs including alendronate," particularly publications concerning the FIT and FLEX studies and that described the appearance of AFFs. Cornell Report at 3, 4–5. He "review[ed] the original trials, the randomized trials, that led to the approval of Fosamax for the treatment of osteoporosis, and then wanted to review many of the case reports, the case series, the summed analysis, and some of the review papers that took all of this information and put it into a more readily digestible form." Cornell Dep. at 56:13–23. Dr. Cornell attempted to "present a balanced analysis" and pointed out studies on both sides of the issue. *Id.* at 58:5–16. He concluded that Fosamax can cause AFFs and "Fosamax use was a substantial contributing factor to Mrs. Glynn's femur fracture." Cornell Report at 4. The methodology Dr. Cornell used is sufficiently reliable because the Bradford Hill criteria are "broadly accepted" in the scientific community "for evaluating causation," *Gannon*, 292 Fed. Appx. at 173 n. 1, and "are so well established in epidemiological research," *In re Avandia Mktg., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, at *3.

*4 Defendant, however, argues that Plaintiffs do not explain the scientific methodology used by Dr. Cornell or show that his methodology is sufficiently reliable. Instead, Defendant asserts that Dr. Cornell's "weight-of-the-evidence" methodology just lists some studies, only some of which support causation, and concludes that the weight of the evidence shows that Fosamax causes AFFs. Defendant explains that this method is inadequate because Dr. Cornell does not discuss how these studies establish causation or why certain studies outweigh others that do not find causation. Additionally, Defendant points out that Dr. Cornell has not done an evaluation of possible biases or confounding factors found in the studies. Because Dr. Cornell does not show that his methodology is sufficiently reliable to show general causation, Defendant argues that he cannot establish specific causation—that Mrs. Glynn's Fosamax use caused her AFF. Defendant explains that the Bradford Hill criteria do not apply to specific causation, and Dr. Cornell's differential diagnosis was unreliable because he did not rule out the possibility that other things could have caused Mrs. Glynn's fracture.

Defendant is free to address these issues on cross-examination, but Defendant's concerns do not prohibit Dr. Cornell from testifying as an expert because he is qualified and the methodology he used is sufficiently reliable. *See Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11, 15 (1st Cir.2011), *cert. denied*, —— U.S. ——, 132 S.Ct. 1002, 181 L.Ed.2d 734 (2012) (stating "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' ").

Regarding Dr. Cornell's specific causation opinion that Fosamax caused Mrs. Glynn's femur fracture, he applied the differential diagnosis method, which is "a technique that involves assessing causation with respect to a particular individual." *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 807 (3d Cir.1997). It "is a process by which a physician rules out alternative causes through review of a patient's medical histories and

records, physical examination of the patient, laboratory testing, study of relevant medical literature, and other techniques." *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liab. Litig.*, 890 F.Supp.2d 552, 561 (E.D.Pa.2012). The "technique is generally accepted in the medical community." *Id.*

Here, Dr. Cornell applied the differential diagnosis method by examining Mrs. Glynn's past medical history and conducting his own examination of her on September 26, 2012, after which he concluded that "[t]o a reasonable degree of medical certainty, Mrs. Glynn suffered a nontraumatic [AFF] in the setting of seven years of full dose Fosamax and alendronate therapy." Cornell Report at 34–36. Dr. Cornell reviewed radiographs taken on April 17, 2009 to evaluate the fracture and reviewed follow-up X-rays, hospital records, rehabilitation records, orthopedics records, prescription records from pharmacies, and deposition transcripts, among other things, in forming his opinion [docket # 109, Ex. 78, Appendix B to Cornell Report]. He ruled out possible alternative causes of Mrs. Glynn's AFF. Cornell Report at 38–40, 42–43, 45–46. Dr. Cornell did not have to "rule out every possible alternative cause of" Mrs. Glynn's AFF; instead, only "[o]bvious alternative causes need to be ruled out." *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir.1999). Thus, Dr. Cornell applied the differential diagnosis method in arriving at his conclusion that Mrs. Glynn's Fosamax use was a substantial contributing factor to her AFF.

*5 Therefore, the methodology used by Dr. Cornell in arriving at both his general and specific causation opinions is sufficiently reliable. Both the Bradford Hill criteria and differential diagnosis are widely used and accepted in the scientific community to arrive at causation opinions.

3. Dr. Cornell's Testimony Fits the Facts of the Case

Finally, Dr. Cornell's testimony fits the facts of the dispute and will assist the trier of fact because Plaintiffs seek to show that Mrs. Glynn's AFF was caused by her Fosamax use and Dr. Cornell not only opines that AFFs are caused by long term bisphosphonate use, like Fosamax, but also that Mrs. Glynn's Fosamax use was a "substantial contributing factor to her" AFF. *See* Cornell Report at p. 22, 47. Consequently, Dr. Cornell's proffered testimony will assist the trier of fact in determining whether Fosamax caused Mrs. Glynn's AFF.

Because Dr. Cornell is qualified, used a methodology that is sufficiently reliable, and his opinion fits the facts of a case, his expert testimony is admissible under *Daubert.*

B. Dr. Klein

Plaintiffs asked Dr. Klein, a pathologist, to offer his opinion on whether Fosamax use causes AFFs and the "mechanism by which those fractures are precipitated" [docket # 103, Ex. 11, Dr. Klein's Report ("Klein Report") at 2].

1. Dr. Klein Is Qualified as an Expert

Dr. Klein is currently the Director of Pathology and Laboratory Medicine at the Hospital for Special Surgery where he has "direct clinical responsibilities for patients ...." *Id.* at 3–4. He also has "direct clinical responsibilities ... as a consultant at Memorial Sloan–Kettering Cancer Center, and as an outside counsel for leading pathology laboratories at major hospitals and institutions around the country." *Id.* at 4. Dr. Klein has reviewed the pathology for at least four patients with AFFs [docket # 105, Ex. 37, Dr. Klein's Deposition ("Klein Dep.") at 41:4–12]. Dr. Klein is currently a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College. Klein Report at 3. He is involved with several publications, including as the lead author and editor of *Non-neoplastic Diseases of Bones and Joints,* the only peer-reviewed, comprehensive textbook on the issue, and as a member of the editorial boards of *Human Pathology, Skeletal Radiology, Advances in Anatomical Pathology,* and *HSS Journal. Id.* Dr. Klein is the Consultant Editor of Research for *The Journal of Bone and Joint Surgery (American)* and has authored or co-authored more than 180 articles, most of which relate to bone pathology. *Id.* Therefore, Dr. Klein possesses "a broad range of knowledge, skills, and training" to qualify him as an expert in pathology. *In re Paoli,* 35 F.3d at 741.

2. Dr. Klein's Methodology Is Sufficiently Reliable

Like Dr. Cornell, Dr. Klein used the Bradford Hill criteria to form his opinion. Klein Report at 2. As discussed above, the Bradford Hill methodology is sufficiently reliable because it is "widely used in the scientific community to assess general causation." *Gannon,* 292 Fed. Appx. at 173. In applying the nine Bradford Hill criteria, Dr. Klein reviewed human and animal studies

and studies performed by Defendant to form his opinion. *See* Klein Report at19–38. The studies revealed a strong association between bisphosphonates, like Fosamax, and microdamage in the bones as well as decreased bone toughness. *See id.* at 20, 25–30, 32. In addition, Dr. Klein noted a strong association between delayed fracture healing, due to altered bone quality, in patients and animals taking bisphosphonates. *Id.* at 23–24, 29. These findings were replicated in several studies discussed in Dr. Klein's report. Moreover, Dr. Klein cited one study which recognized the "*duration*-dependent, as well as dose-dependent, effect bisphosphonates have on the skeleton." *Id.* at 27. Another study mentioned in Dr. Klein's report noted that the "cessation of bisphosphonate treatment may be prudent for women on therapy who sustain a nonvertebral fracture." *Id.* at 30. Thus, Dr. Klein applied the Bradford Hill criteria, including the strength of association, replication of findings, dose-response relationship, and cessation of exposure factors.

***6** Based on his review of the studies, Dr. Klein concluded that "alendronate significantly alters the cellular properties of bisphosphonate-treated bone." *Id.* at 38. AFFs are not

> attributed to low bone mass or osteoporosis alone, indicative of bone that has fundamentally compromised bone microstructure. Unless a damaging force exerts tension across the entire cortex, the laws of physics and biomechanics as applied to bone further support the conclusion that bone quality and microstructure must be fundamentally compromised for a transverse fracture in a hollow cylinder[, like the femur,] to follow.
>
> [*Id.*]

Thus, Dr. Klein opined that there is a causal relationship between Fosamax and AFFs. *Id.* at 2. He used a sufficiently reliable methodology, the Bradford Hill criteria, in forming this opinion.

Defendant, however, argues that the Bradford Hill criteria apply to epidemiology studies, which Dr. Klein's report does not discuss. Defendant contends that Dr. Klein has not provided support for the proposition that a general causation conclusion can be established using the Bradford Hill criteria and human or animal biopsy data. In addition, Defendant asserts that if Dr. Klein discussed epidemiology studies in his report, he did not demonstrate that he is qualified to interpret that evidence because he has no expertise in epidemiology and does not understand the most basic epidemiology terms. Moreover, Defendant points out that Dr. Klein conceded that the mechanism regarding how bisphosphonates cause AFFs has not been established and that the theories Dr. Klein uses to support his conclusion about mechanism—microdamage, decrease in tissue heterogeneity, bone brittleness, and delayed healing—have not been proved with human data.

Yet, Dr. Klein has properly applied the Bradford Hill criteria to epidemiological studies. Epidemiological studies include randomized trials in which one group is exposed to an agent, such as Fosamax, and another group is not, and the effect of the agent or lack thereof is observed. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 555–56. Here, Dr. Klein examined randomized trials, such as Dempster et al., Boskey et al., and Donnelly et al.; in each of these studies, some women were given alendronate or another bisphosphonate and others were not. Klein Report at 20–21. Moreover, the Federal Judicial Center's Reference Manual on Scientific Evidence states that "toxicology models based on live animal studies ... may be used to determine toxicity in humans" in addition to observational epidemiology. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 563.

For his testimony to be admissible, Dr. Klein is not required to show that the mechanism has been definitely established. Instead, he just needs to show that the methodology he used to arrive at his opinion is sufficiently reliable. *See Milward,* 639 F.3d at 15 (stating "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' "). Dr. Klein arrived at his opinion on the mechanism by examining several studies and using a scientific method that is sufficiently reliable.

3. Dr. Klein's Testimony Fits the Facts of the Case

***7** Lastly, Dr. Klein's testimony fits the facts of the dispute and will assist the trier of fact. *See Jones,* 2010 WL 3311840, at *4. Through Dr. Klein's testimony, Plaintiffs seek to show that Fosamax causes AFFs and

the mechanism by which this happens. *See* Klein Report at 2. Dr. Klein opines that Fosamax causes AFFs and discusses several ways this happens—microdamage, abnormal osteoclasts, altered bone quality, and delayed fracture healing. Thus, Dr. Klein's testimony will assist the trier of fact in determining whether Fosamax causes AFFs, the ways in which this happens, and ultimately, his testimony will aid the jury in deciding whether Mrs. Glynn's Fosamax use caused her AFF.

C. Dr. Madigan

Plaintiffs asked Dr. Madigan, a statistician, to give his opinion regarding "whether a signal of problematic oversuppression of bone turnover and associated [AFF] ... existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same" and "assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis" [docket # 33, Ex. 30, Dr. Madigan's Report ("Madigan Report") at ¶ 5].

1. Dr. Madigan Is Qualified as an Expert

Dr. Madigan is Professor and Chair of Statistics at Columbia University. *Id.* at ¶ 1. He is an elected Fellow of the Institute of Mathematical Statistics and the American Statistical Association, and from 1995 to 2005 was the 36th most cited mathematician worldwide. *Id.* In 2010, he completed a term as Editor of the journal *Statistical Science*. *Id.* Dr. Madigan has consulted for companies such as Novartis, Pfizer, and Sanofi–Aventis on several issues, "many related to drug safety." *Id.* at ¶ 2. He has statistical experience with clinical trials and has published more than 100 technical papers on many topics, including pharmacovigilance [3]. *Id.*

Within the last few years, drug safety "with a focus on the development and application of statistical methods for pharmacovigilance" has been "one of [Dr. Madigan's] significant research interests ...." *Id.* at ¶ 3. He has published work in several journals, including *Drug Safety, Pharmacoepidemiology and Drug Safety,* and *Epidemiology*. *Id.* Dr. Madigan is an investigator in the Mini–Sentinel project, which is "a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products." *Id.* He is the "methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry, which addresses "research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market." *Id.* Dr. Madigan is a member of the FDA's Drug Safety and Risk Management Committee, which "advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility." *Id.* Dr. Madigan is qualified as an expert because he has "a broad range of knowledge, skills, and training [to] qualify ... [him] as such." *In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Madigan's qualifications.

2. Dr. Madigan's Methodology Is Sufficiently Reliable

*8 Dr. Madigan examined the FDA's Adverse Event Reporting System ("AERS") database for a "possible association between Fosamax and a series of ... terms selected by Merck to evaluate oversuppression of bone turnover and associated" AFFs. Madigan Report at ¶ 25. The terms were: bone development abnormal, bone disorder, bone formation decreased, fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, fracture, and femur fracture. *Id.* at ¶ 26. Dr. Madigan used "two industry-standard signal detection algorithms ... to assess whether or not Fosamax presented a safety signal" indicating oversuppression of bone turnover or AFFs. *Id.* at ¶ 25. The QScan pharmacovigilance software computed the statistics. *Id.* at ¶ 27. Dr. Madigan then compared the Fosamax signals to other oral bisphosphonates and a non-bisphosphonate used for the treatment and prevention of osteoporosis. *Id.* at ¶ 25. After reviewing the data, Dr. Madigan opined that

> industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the

> spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.
>
> [*Id.* at ¶ 36.]

This opinion is admissible because it is based on a method that is sufficiently reliable. *See Jones,* 2010 WL 3311840, at *4. Two factors that a court may take into consideration in determining reliability is whether the methodology has been subjected to peer review and publication and whether there is general acceptance in the scientific community. *Daubert,* 509 U.S. at 593–94. Here, Dr. Madigan's method, data mining in pharmacovigilance, is generally accepted in the scientific community and has "become routine both in the pharmaceutical industry and amongst regulators worldwide." Madigan Report at ¶ 8. In fact, "[p]harmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice." *Id.* at ¶ 9. "SRS systems provide the primary data for day-to-day drug safety surveillance by regulators and manufacturers worldwide." *Id.* at ¶ 14. In addition, the QScan software Dr. Madigan used in formulating his opinion is generally accepted by the scientific community because it "has been in widespread use for over 10 years and has been validated extensively." *Id.* at ¶ 28. Moreover, "[m]any peer-reviewed publications report results derived from QScan." *Id.* Thus, Dr. Madigan's methodology is sufficiently reliable.

***9** Although Defendant argues that Dr. Madigan's methodology is unreliable because he did not review the substance of the adverse event reports to see if they actually involve AFFs or oversuppression of bone turnover, this argument is inappropriate on a *Daubert* motion. Dr. Madigan's testimony will be subject to cross-examination, and the credibility of his opinion will be ultimately determined through the adversarial process. Dr. Madigan's methodology is sufficiently reliable because it is generally accepted in the scientific community, and therefore, Plaintiffs have satisfied the second prong of *Daubert.*

3. Dr. Madigan's Testimony Fits the Facts of the Case

Lastly, Dr. Madigan's testimony fits the facts of the case and will assist the trier of fact because it is related to Plaintiffs' failure to warn claim. *See Jones,* 2010 WL 3311840, at *4. A failure to warn claim requires a plaintiff to show "(1) that a manufacturer has a duty to warn (2) against dangers resulting from foreseeable uses about which it knew or should have known and (3) that failure to do so was the proximate cause of the harm." *In re Fosamax Prods. Liab. Litig.,* 2013 WL 76140, *3 (S.D.N.Y. Jan.7, 2013). Dr. Madigan's testimony fits the facts of this case because he opines that "[a]s early as 2001–2002, the spontaneous report data for Fosamax provide[d] signals for a number of indicators of suppression of bone turnover," meaning Defendant knew or should have known that Fosamax caused certain dangers in 2001–2002, thus imposing on Defendant a duty to warn of those dangers. Madigan Report at ¶ 36.

Defendant, however, argues that Dr. Madigan's testimony does not fit the facts of the case because it is irrelevant since there is no reasonable standard of care that would have required Defendant to conduct data mining. This is also a matter best left to the credibility determination of the jury.

As a result, Dr. Madigan's expert testimony is admissible under *Daubert* because he is qualified, he used a sufficiently reliable methodology, and his opinion fits the facts of the case.

D. Dr. Blume

Dr. Blume is offered as an expert in pharmacovigilance and FDA regulation. Plaintiffs offer the testimony of Dr. Blume to: (1) "address the timeliness and completeness of the efforts undertaken by [Defendant] ... to fully inform prescribers and patients of the increasingly adverse benefit risk assessments associated with long-term Fosamax use in postmenopausal women"; (2) "evaluate the negative consequences of protracted bone oversuppression," including AFFs, in people receiving Fosamax; and (3) "to consider the pharmacovigilance activities undertaken by [Defendant] to evaluate the noted adverse events during the relevant time periods" [docket # 119, Ex. 33, Dr. Blume's Report ("Blume Report") at ¶ 6].

1. Dr. Blume is Qualified as an Expert

Dr. Blume received her Ph.D. in Pharmacology and Toxicology from the West Virginia University

Medical Center and is currently the President of Pharmaceutical Development Group, Inc. (PDG), "a consulting firm ... specializing in pharmaceutical development and registration activities." *Id.* at ¶ 1. In this role, she "has been responsible for preclinical and clinical (Phases I–IV) programs associated with pharmaceutical product development and the securing of pre-marketing approvals" for many drugs before the FDA. *Id.* at ¶ 2. Additionally, Dr. Blume has directed "all phases of interactions with [the] FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements to New Drug Applications (sNDAs), and the associated approval procedures," including "the collection and evaluation of postmarketing adverse medical events, the preparation of updated product labeling, and the dissemination of accurate, complete and timely product-related information to health care providers." *Id.* at ¶ 3. She was responsible for "regulatory review of promotional and education materials for both brand-name and generic drug products." *Id.* Dr. Blume's responsibilities include the "design, execution, and interpretation of pivotal safety-related trials and the development and implementation of pharmacovigilance procedures intended to detect new safety signals and track the evolution of previously identified signals." *Id.* at ¶ 4. She has directed "all phases of interactions with the FDA relating to post-approval labeling procedures regarding changes to safety-related information based upon postmarketing signal tracking and pharmacovigilance efforts," including "collection and evaluation of postmarketing adverse medical events, review and interpretation of the results of postmarketing clinical studies, the preparation of updated product labeling and other communication tools, and the dissemination of new product information to health care providers, patients, and consumers." *Id.* at ¶ 5. Dr. Blume possesses the knowledge, skills, and training necessary to qualify her as an expert. *See In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Blume's qualifications.

2. Dr. Blume's Methodology Is Sufficiently Reliable

***10** Dr. Blume reviewed published studies (Blume Report at ¶¶ 57–74), Merck's Period Safety Update Reports (*id.* at ¶ 75), Dr. Madigan's report (*id.* at ¶¶ 76–78), Merck's Worldwide Adverse Experience System ("WAES") (*id.* at ¶ 79), and epidemiological studies (*id.* at ¶¶ 82–90). *See also* docket # 119, Ex. 5, Dr. Blume's Deposition ("Blume Dep.") at 148:9–18; 338:9–20 (stating that she looked at the WAES database, literature reports, epidemiological studies, the AERS database, and Dr. Madigan's report). She discussed the "specific regulatory procedures and regulations" pharmaceutical manufacturers have to comply with, including procedures and regulations related to FDA approval, labeling, postmarketing surveillance, and reporting requirements. *Id.* at ¶¶ 11–34. Dr. Blume evaluated all of this information using "her years of experience" in "the industry," *see In re Viagra Products Liability Litigation,* 658 F.Supp.2d 950, 962 (D.Minn.2009), and opined that

> the scientific literature, Merck's internal adverse event database, the AERS database, and epidemiology analyses confirmed the increasingly adverse risk-benefit profile related to long-term Fosamax use in the indicated populations. However, Merck permitted their labeling and other prescriber information to remain static with respect to both the deteriorating risk-benefit assessment and the escalation in ... [AFF] reports. Such omissions do not comply with the regulatory and industry standards of responsible pharmaceutical companies .... Merck also should have undertaken timely and adequate studies to more clearly elucidate the risks of Fosamax use in the various indicated populations. Finally, Merck should have disseminated Dear Healthcare Professional Letters to advise prescribers and their patients of the escalating safety and efficacy concerns. Merck's omissions have likely resulted in the exposure of numerous patient populations to unnecessary risks associated with the initiation and ongoing treatment with Fosamax.
>
> [Blume Report at ¶ 110.]

Dr. Blume states that "[b]y the early 2000's, it was known that ... [AFFs] were clinically significant events ...." *Id.* at ¶ 109. Dr. Blume opines that Defendant should have changed the Fosamax label "to include escalating warning and precautionary risk information related to" AFFs. *Id.* Instead, Dr. Blume notes that Defendant "did not identify these fractures in the labeling until 2009" even though it received reports that AFFs were "associated with Fosamax use as early as 2002." *Id.* at ¶¶ 31, 82.

Defendant argues that the Court should exclude Dr. Blume's opinions on: (1) the legal requirements governing pharmaceutical manufacturers and Defendant's compliance with those requirements; (2) Defendant waiting too long to add information about femur fractures

to the Adverse Reactions section of the label; (3) Defendant failing to add a warning or precaution about femur fractures to the Fosamax label before 2009; (4) Defendant's failure to timely investigate a potential link between Fosamax and AFF; (5) Defendant's alleged motives or state of mind; (6) the causation or mechanism of AFF; and (7) the drug Evista is safer than Fosamax. Yet, because *Daubert* concerns the narrow issue of whether expert testimony is admissible, this is not the appropriate time for Defendant to request that the Court preclude Dr. Blume from testifying about certain topics. Defendant may question Dr. Blume's opinions or methodology on cross-examination. *See Milward,* 639 F.3d at 15 (stating "[s]o long as an expert's scientific testimony rests upon "good grounds," based on what is known, ..., it should be tested by the adversarial process, rather than excluded").

***11** Despite Defendant's issues with Dr. Blume's opinions, Plaintiffs have satisfied the second prong of *Daubert* because Dr. Blume's methodology is sufficiently reliable.

3. Dr. Blume's Testimony Fits the Facts of the Case

Dr. Blume's testimony fits the facts of the case because she opines that it was known in the early 2000's that AFFs were associated with Fosamax use. *See* Blume Report at ¶¶ 31, 82. Dr. Blume's testimony is relevant and will assist the trier of fact in deciding Plaintiffs' failure to warn claim because Dr. Blume's opinion is relevant to whether and when Defendant knew or should have known that AFFs were associated with Fosamax and therefore, when Defendant should have sought a label change. *See Schneider,* 320 F.3d at 404 (recognizing that expert testimony must "be relevant for the purposes of the case and must assist the trier of fact").

E. Treating Physicians

Defendant argues that the Court should preclude causation testimony from Plaintiffs' treating physicians —Drs. Busch, Lindsay, Fletcher, and Limes—because: (1) Plaintiffs have not provided Rule 26 disclosures for any of the treating physicians; and (2) none of the treating physicians are able to offer a reliable causation opinion to a reasonable degree of medical certainty. Plaintiffs, however, assert that they do not intend to elicit expert testimony from the treating physicians; instead, the treating physicians will testify about Mrs. Glynn's care and treatment, which does not require Rule 26 disclosures.

Treating "physicians are not required to submit expert reports when testifying based on their examination, diagnosis and treatment of a patient." *Patterson v. Howard,* 2010 WL 1050052, *4 (D.N.J. Mar.18, 2010). Federal Rule of Civil Procedure 26(a)(2)(B) requires a witness to submit a written report only "if the witness is one retained or specially employed to provide expert testimony in the case or one whose duties as the party's employee regularly involve giving expert testimony." A "treating physician is not necessarily retained or specially employed to provide expert testimony simply because he or she proffers on causation and prognosis" because "doctors may need to determine the cause of an injury in order to treat it." *Pease v. Lycoming Engines,* 2012 WL 162551, *12 (M.D.Pa. Jan.19, 2012). In order to "determine whether a party retained or specially employed a treating physician to provide expert testimony," the Court must examine "whether the treating physician acquired his opinion as to the cause of ... plaintiff's injuries directly through his treatment of the plaintiff." *Id.* (internal quotation omitted). As a result, treating physicians are not required to submit expert reports "if they form their opinion on causation or prognosis as part of the ordinary care of a patient." *Id.*

Therefore, the testimony of Drs. Busch, Lindsay, Fletcher, and Limes is appropriate if it is based on their care and treatment of Mrs. Glynn. This Court will not allow, however, any expert testimony on causation from these physicians.

II. CONCLUSION

***12** For the reasons outlined above, this Court denies Defendant's *Daubert* Motion as to Drs. Cornell, Klein, Madigan, and Blume. An appropriate Order accompanies this Opinion.

All Citations

Not Reported in F.Supp.2d, 2013 WL 1558690, 91 Fed. R. Evid. Serv. 106

Footnotes

1 The abbreviation of atypical femur fracture (singular) is "AFF."

2 Db13 means page 13 of Defendant's brief.

3 Pharmacovigilance is the surveillance of spontaneous reporting system ("SRS") databases "for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency." *Id.* at ¶ 7.

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